

TREATMENT OF ALLERGIC AND VASOMOTOR RHINITIS

A clinical and experimental study with topical
use of disodium cromoglycate, beclomethasone
dipropionate and β -adrenoceptor stimulants

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Lund 1981

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The present thesis is based on the following papers which will be referred to in the text by Roman numerals:

- I. Löfkvist, T., Rundcrantz, H. & Svensson, G.
Treatment of vasomotor rhinitis with intranasal disodium cromoglycate (SCG).
Results from a double-blind cross-over study.
Acta Allergologica 32: 35-43, 1977
- II. Löfkvist, T. & Svensson, G.
Treatment of vasomotor rhinitis with intranasal beclomethasone dipropionate (Becotide^R).
Results from a double-blind cross-over study.
Acta Allergologica 31: 227-238, 1976
- III. Svensson, G., Hegardt, B. & Löfkvist, T.
Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131.
I. Normal persons and hay fever patients in asymptomatic period.
Acta Otolaryngologica (Stockholm) 90: 297-303, 1980
- IV. Svensson, G.
Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131.
II. Nasal provocation tests with hay fever patients in asymptomatic period.
Acta Otolaryngologica (Stockholm) 90: 130-138, 1980



V. Svensson, G., Hegardt, B. & Löfkvist, T.
Influence of a β -adrenoceptor stimulant, KWD 2131,
on nasal histamine provocation tests.
Rhinomanometric evaluations in normal persons and
patients with hay fever.
Acta Otolaryngologica (Stockholm). Accepted for
publication.

VI. Svensson, G.
Topical treatment of seasonal allergic rhinitis
with a β -adrenoceptor stimulant (KWD 2131).

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INTRODUCTION

A. Anatomical and physiological features of the nasal mucosa

Among other structures, nerves, glands, vessels and mast cells are embedded in the nasal mucosa. Disturbances of these structures are reflected by nasal symptoms characterizing allergic as well as vasomotor rhinitis. The following description is based on findings in animal and man.

The nasal mucosa is sensory-innervated by the trigeminal nerve. The motor impulses to the mucosa are transmitted by sympathetic as well as parasympathic nerve fibres. The glands are mostly supplied by parasympathic fibres and the vessels by sympathetic as well as parasympathic fibres (Cauna et al., 1972; Ishii, 1980). The adrenergic system includes at least two forms of receptors, α - and β -adrenoceptors (Ahlquist, 1948). The α -adrenoceptors induce contraction and the β -adrenoceptors relaxation of the smooth muscle in vessels (Mellander & Johansson, 1968). The function of α -adrenoceptors dominates in the nasal mucosa (Hall & Jackson, 1968; Änggård & Edwall, 1974); the existence of β -adrenoceptors have been demonstrated in experiments in animals (Malm, 1974 b; Hiley et al., 1978). Stimulation of α -adrenoceptors induces contraction of the nasal vessels and decreases the blood content in the nasal mucosa (Hall & Jackson, 1968; Malm, 1974 a). β -adrenoceptors, if they exist in the human nasal mucosa, might induce relaxation with increased blood content at stimulation. Parasympathic stimulation too gives rise to increasing nasal blood content and also induces increased glandular secretion (Malcomson, 1959; Änggård, 1974).

VIP-positive (Uddman et al., 1978; Ånggård, 1979) and substance P-positive nerves (Ånggård, 1979) have also been identified in the nasal mucosa. The importance of these for normal and pathological regulation of the nasal functions is unknown.

Mast cells are widely distributed in the nasal mucosa. The biologic function of mast cells, highly relevant to allergic processes, is the release of inflammatory mediators such as histamine, SRS-A (leukotriene), eosinophilic chemotactic factor, platelet-activating factor and kallikrein. Several mechanisms, both immunological (antigen-induced) and non-immunological, have been described for the release of mediators (cf. Plaut & Lichtenstein, 1978).

B. Pathophysiology of allergic and vasomotor rhinitis

The normal regulation of the nasal mucosa is disturbed in allergic and vasomotor rhinitis. Both conditions are symptomatologically characterized by varying degrees of nasal secretion, nasal obstruction, nasal itching, and sneezing despite different pathophysiology.

1. Allergic rhinitis

After penetration through mucosal surfaces the allergens stimulate transformation of immunocompetent lymphocytes to plasma cells which synthesize IgE antibodies (reagins). After transport via the blood most of the reagins adhere to mast cells, among others. Renewed allergen exposure and interaction between allergen and IgE-mast-cell complexes activate a series of intracellular reactions. After the final reaction mediators, such as histamine, are secreted from the mast cells. The release of mediators is modulated by several mechanisms. Factors increasing intracellular CAMP are assumed to

suppress the mediator release. Histamine, a main mediator, stimulates receptors in the nasal mucosa and thereby induces vasodilation and increased vasopermeability as well as secretion with nasal congestion (increased blood content and oedema) and discharge as consequences. Stimulation of sensory nerve fibres triggers nasal itching and sneezing (cf. Plaut & Lichtenstein, 1978).

2. Vasomotor rhinitis

The pathophysiology of vasomotor rhinitis is unknown. The condition is commonly defined as an unspecific hyperreactivity on the part of the nasal mucosa and there is no demonstrable evidence of allergy.

The nasal mucosa in patients with vasomotor rhinitis is morphologically uniform with that of patients with allergic rhinitis - oedema and dilated vessels (Jahnke et al., 1977). An imbalance of the autonomic nervous system can partially explain these findings and the clinical manifestations of vasomotor rhinitis. Patients with vasomotor rhinitis are often classified according to their dominating symptoms in blockers, runners and sneezers. An increased parasympathic activity, with stimulation of the nasal glands, is given as the reason for the nasal discharge in runners (Änggård, 1979) while the symptoms in blockers may be explained by a decreased sympathetic (Jahnke & Theopold, 1977) or an increased parasympathic (cf. Taylor, 1973) activity.

Apart from this, nerves containing substance P and VIP, both potent vasodilators, are observed in the nasal mucosa and may be responsible for parts of the nasal obstruction in vasomotor rhinitis. Kallikrein-like substance (Eccles & Wilson, 1973) and SRS-A-like activity (Änggård & Strandberg, 1981) found in nasal secretion, are other sources of interference with the nasal regula-

tion. Our environment contains histamine liberators (Zuskin & Bouhuys, 1974; Slavin, 1980), and a non-immunological release of histamine from nasal mast cells may be a further explanation of the symptoms in vasomotor rhinitis. Thus, several mechanisms for inducing the symptoms of vasomotor rhinitis are present but the functional importance and sequence of these and probably other factors have not been established.

C. Principles for pharmacological treatment of allergic and vasomotor rhinitis

The pathophysiology of allergic as well as vasomotor rhinitis implies several possibilities for pharmacological treatment and the therapeutic arsenal includes drugs with mast-cell-stabilizing ability, histamine-receptor-blocking capacity, α -adrenoceptor-stimulating action, antiinflammatory effect, oedema-reducing property and combinations of these.

Different ways for administration of drugs are available. Topical treatment of bronchial asthma (cf. Brogren et al., 1974 a, 1975 a; Leifer & Wittig, 1975) has been successful during the last decade. Local treatment of nasal disorders seems also advantageous as drugs can easily be applied in the nose, small amounts of the substances can be used with reduced risks of general side effects, and local changes of the nasal mucosa can easily be disclosed and evaluated. Some substances with presumably proper pharmacological qualities for treatment of allergic and vasomotor rhinitis and suitable pharmaceutical properties for nasal application are therefore investigated. Two of them - disodium cromoglycate (SCG) and beclomethasone dipropionate (BDP) - had been used in earlier studies but these were found to be incomplete with regard to the number of

patients and the time of observation. Two other drugs - terbutaline and KWD 2131 - both acting as β -adrenoceptor stimulants, had never been tried in allergic rhinitis.

1. Disodium cromoglycate (SCG)

The precise mode of action of SCG is not known, but the substance is considered as a mast-cell-stabilizing agent at reagin-mediated reactions. It also inhibits histamine release caused by non-antigenic stimuli (cf. Brogden et al., 1974 a).

For more than 10 years SCG has been used successfully in the treatment of patients with allergic bronchial asthma. In a lower degree it is effective also in cases of intrinsic asthma and exercise-induced asthma (Poppius et al., 1970; Munro-Ford, 1971; Silverman & Turner-Warwick, 1972). Vasomotor rhinitis is often regarded as a disease in the upper airways corresponding to intrinsic asthma in the lower airway, as both diseases simulate allergic conditions but with negative findings at allergological examination. It is therefore conceivable that SCG might be effective also in cases of vasomotor rhinitis. An indication of such a capacity was also provided by favourable therapeutic effects of SCG in patients with perennial rhinitis, i.e. a material including both allergic individuals and people without evidence of allergy (Holopainen et al., 1972; Hopper & Dawson, 1972; Mygind et al., 1972).

2. Beclomethasone dipropionate (BDP)

Corticosteroids, administered perorally or as injections, have a favourable effect in allergic as well as vasomotor rhinitis. Several mechanisms have been suggested as possible explanations for the antiallergic effect. The most likely possibility is an antiinflammatory

effect (cf. Morris, 1978). The use of corticosteroids in allergic and vasomotor rhinitis has been restricted due to their reputation of causing side effects. Topical administration offers the possibility of limiting corticosteroid action to the site of application and avoiding the adverse effect of systemic therapy. For nearly 30 years attempts have been made to treat asthma and rhinitis by local application of corticosteroids. None of these attempts were successful due to absorption to the systemic circulation until the preparation of betamethasone valerate and beclomethasone dipropionate (BDP) became available.

Treatment of bronchial asthma and allergic rhinitis with BDP (cf. Brogden et al., 1975 a,b) has been successful using doses without systemic effect. Since there was a favourable local effect in patients with perennial rhinitis (Gibson et al., 1974; Hansen & Mygind, 1974) a similar action of the substance could also be expected in vasomotor rhinitis.

3. Terbutaline

Terbutaline, a selective β_2 -adrenoceptor stimulant, relaxes bronchial smooth muscle and is successfully used in treatment of bronchial asthma. Besides the bronchodilating action, terbutaline also possesses antiallergic, oedema-reducing and cardiovascular effects. The antiallergic capacity has been considered to be dependent on stimulation of β -adrenoceptors on the surface of mast cells leading to increased intracellular concentration of cyclic AMP and reduced release of mediators (cf. Holroyde et al., 1977). The antiallergic effect of β -adrenoceptor stimulants in cases of bronchial asthma is difficult to assess because the relief of symptoms at bronchial allergen challenges can also be attributed to the relaxant

effect on bronchial smooth muscle. The absence of such a mechanism in the upper airway should give better possibilities for in-vivo evaluations of the antiallergic effect of β -adrenoceptor stimulants in the nasal cavities than in the lungs.

An anti-oedematous activity has been demonstrated for terbutaline in animal experiments. It was speculated that there may be a similar effect also on the oedema in the lower airways at bronchial asthma (O'Donnell & Persson, 1978; Persson et al., 1978, 1979). Thus, an antiallergic action of β -adrenoceptor stimulants might be due to decreased release of mediators (mainly histamine) and/or an inhibition of histamine-induced microvascular leakage. Also the assessment of an anti-oedematous effect of β -adrenoceptor stimulants in bronchial asthma involves methodological difficulties - again due to the simultaneous bronchorelaxation - while the nasal mucosa seemed to be a suitable object of such investigations.

4. KWD 2131 /1-(3,5-dihydroxyphenyl)-2-[(1,1-dimethyl-2-hydroxyethyl)-amino] ethanol sulphate/
KWD 2131, a new β -adrenoceptor stimulant, is structurally related to terbutaline. It exhibits the usual effects of β -adrenoceptor stimulants, but its profile of action is different from that of terbutaline (Sörenby, 1977).

In animals, KWD 2131 shows appreciable antiallergic effects in concentrations producing weak tracheorelaxation and cardiovascular effects. The antiallergic effect as well as the tracheorelaxation of terbutaline are documented in the same concentration range (Sörenby, 1977). In man, the potency of KWD 2131 with regard to cardiovascular effect is about one tenth of that for terbutaline (Pegelow & Strandberg, 1978). Thus, in-

creasing doses of KWD 2131 would imply an expedient antiallergic effect without troublesome side effects. KWD is thus an interesting tool for assessment of the antiallergic capacity of β -adrenoceptor stimulants.

AIMS OF THE STUDY

The common feature of the present investigation is nasal application of various substances. The objectives were to assess:

- (1) Symptom-relieving action and adverse effects of disodium cromoglycate (I) and beclomethasone dipropionate (II) in patients with vasomotor rhinitis;
- (2) Nasal and general reactions to different doses of β -adrenoceptor stimulants (terbutaline and KWD 2131) in normal subjects and asymptomatic (out of season) patients with seasonal allergic rhinitis (III);
- (3) Antianaphylactic effect of various doses of terbutaline and KWD 2131 on symptoms induced in patients with seasonal allergic rhinitis (IV);
- (4) Inhibitory action of KWD 2131 on histamine-induced nasal reactions in normal subjects and patients with seasonal allergic rhinitis (V);
- (5) The clinical value of KWD 2131 during the grass-pollen season in patients with hay fever (VI).

MATERIAL AND METHODS

Study I: Forty-nine adult patients with vasomotor rhinitis were treated intranasally during 13 (6 + 1 + 6) weeks with 40 mg disodium cromoglycate and placebo in a randomized double-blind cross-over study.

The results were based on data from diary cards, the patients' preferences for treatment period, findings at rhinoscopy, cultures of bacteria from the nasopharynx and different haematological analyses.

Study II: Thirty-nine adult patients with vasomotor rhinitis were treated during 9 (4 + 1 + 4) weeks with 300 µg beclomethasone dipropionate and placebo intranasally in a randomized double-blind cross-over study.

The results were based on data from diary cards, the patients' preferences for treatment period, findings at rhinoscopy, cultures of bacteria as well as fungi, and haematological analyses including estimations of cortisol in plasma.

Study III: Sixteen adult normal persons and 13 adult patients with hay fever participated during asymptomatic periods in a randomized placebo-controlled double-blind cross-over study and were investigated with regard to the action of nasal application of two β -adrenoceptor stimulants (terbutaline: 0.5 as well as 5 mg, and KWD 2131: 1.25 as well as 5 mg to each nasal cavity).

The results were based on rhinomanometric measurements, findings at rhinoscopy, the participants' subjective evaluation of various nasal symptoms, determinations of pulse frequency and examination of hand tremor.

Study IV: Thirteen adult patients with hay fever participated during asymptomatic periods in a randomized placebo-controlled double-blind cross-over study and were investigated with respect to the prophylactic action of nasal application of two β -adrenoceptor stimulants (terbutaline: 0.5 as well as 5 mg, and KWD 2131: 1.25 as well as 5 mg to each nasal cavity) at nasal provocations with the appropriate allergen.

The results were based on rhinomanometric measurements, findings at rhinoscopy, counting of sneezing attacks, the patients' subjective evaluation of various nasal symptoms, determinations of pulse frequency and examination of hand tremor.

Study V: Eleven adult normal persons and 11 patients with hay fever participated during asymptomatic periods in a randomized placebo-controlled double-blind cross-over study and were investigated with respect to the prophylactic action of nasal application of a β -adrenoceptor stimulant, KWD 2131, (5 mg to each nasal cavity) at nasal histamine provocations.

The results were based on rhinomanometric measurements, findings at rhinoscopy, counting of sneezing attacks and the participants' subjective evaluation of various nasal symptoms.

Study VI: Twenty-seven adult patients with hay fever, triggered by grass pollen, were treated during 4 (2 + 2) weeks of the grass-pollen season with 30 mg KWD 2131/day (5 mg x 2 x 3) and placebo intranasally, in a randomized double-blind trial, designed for cross-over as well as comparative evaluations. Data were obtained from a simultaneous grass-pollen count.

The results were based on data from diary cards, the patients' preferences for treatment periods, findings at rhinoscopy and several analyses of blood and urine.

RESULTS

Study I: Extensive statistical analyses of data from diary cards, findings at rhinoscopy, and patients' preferences could not demonstrate disodium cromoglycate to be superior to placebo in symptom-relieving action in patients with vasomotor rhinitis. These results were valid for the whole material as well as for the subgroups "blockers", "runners", "blockers and runners", "patients with sneezing and itching" and "patients with high eosinophilic count in nasal smear". However, some patients distinctly felt that the symptoms improved more with disodium cromoglycate than with placebo.

The nasopharyngeal flora was not changed by disodium cromoglycate and the haematological analyses remained normal during both treatment periods.

Study II: About 64% of the patients with vasomotor rhinitis preferred the treatment with beclomethasone dipropionate, 13% the treatment with placebo, and 23% did not find any differences between the two forms of treatment. About 74% of the patients considered themselves free from trouble or improved during the treatment with beclomethasone dipropionate, while 69% experienced no change at all or a change for the worse during the placebo period.

From the diary card data, significant differences in relief of symptoms were found between treatment with beclomethasone dipropionate and placebo for the symptom sneezing during the first week, for nasal secretion, nasal itching, nasal blocking and all symptoms together during week 2, 3, 4 and 2, respectively.

Rhinoscopy revealed no mucosal changes with either treatment. Cultures for bacteria and *Candida albicans* from nasopharyngeal secretions were generally negative and without evident differences between the two types of treatment.

Morning plasma cortisol level in 19 patients did not differ during the beclomethasone dipropionate period from that during the placebo period.

Study III: Local application of 0.5 mg terbutaline and 1.25 mg KWD 2131 induced no changes in the nasal airway resistance in the normal persons and the asymptomatic patients with hay fever. With 5 mg terbutaline and 5 mg KWD 2131 significant increases in nasal airway resistance were found in both groups when the elevations were analysed for each drug. In comparison with placebo only the increases at the registrations 15 and 20 min after application of terbutaline and KWD 2131 were significant in the normal persons. For the allergic patients a corresponding significant difference was noted 10 min after application of the substances.

The rhinoscopic examination revealed no alterations of nasal mucosa by either substance, and the participants experienced no nasal changes during the experiments.

The high dose of terbutaline (5 mg) induced tachycardia and tremor in all patients as early as 5 min after application of the drug, and these complaints remained during the whole experiments.

Study IV: The nasal provocations with the appropriate allergen on paper discs were followed by marked increases in nasal airway resistance. These increases were distinctly higher than those induced by the paper discs

soaked in Coca's solution.

The rhinoscopic findings and the patients' subjective opinion supported the rhinomanometric determinations.

Pretreatment with KWD 2131 1.25 mg, terbutaline 0.5 mg, KWD 2131 5 mg, and terbutaline 5 mg to each nasal cavity were followed in the given sequence by gradually diminishing increases in the mean of nasal airway resistance. Compared with placebo pretreatment, 5 mg terbutaline and 5 mg KWD 2131 elicited significantly lower increases of nasal airway resistance at the allergen challenges. A reduced increase was also found after 0.5 mg terbutaline, but this effect was less marked. Thus, the best protection was given by 5 mg terbutaline and 5 mg KWD 2131.

The rhinoscopic examination and the patients' own opinion about the symptoms after nasal allergen provocations revealed no evident differences between pretreatment with terbutaline, KWD 2131 or placebo.

Increased pulse frequency and hand tremor were found in all patients when 5 mg terbutaline was administered to each nasal cavity. One patient was troubled by tremor also after administration of the low dose (0.5 mg) of terbutaline and the high dose (5 mg) of KWD 2131.

Study V: The nasal applications of histamine on paper discs in both normal persons and patients with hay fever were followed by significant increases in nasal airway resistance. These elevations were distinctly higher than those induced by the paper discs soaked in Coca's solution.

The rhinoscopic findings and the patients' subjective opinion supported the rhinomanometric determinations.

Pretreatment with 5 mg KWD 2131 and placebo did not affect the outcome of histamine challenges, neither in rhinomanometric determinations nor in rhinoscopic findings or the volunteers' subjective opinion about the symptoms.

Study VI: The hay-fever patients' subjective evaluation of the treatment with KWD 2131 and placebo during the grass-pollen season did not reveal any differences between the two forms of medication.

Statistical analyses of the notes on the diary cards did not prove any sure prophylactic effect of KWD 2131, neither in days with a high number of grass pollen in the air nor in days with low pollen count.

At rhinoscopic examination no differences, as regards oedema and secretion, were observed between the treatment with KWD 2131 and placebo.

No sure side effects were experienced by the patients except hand tremor in one case. All laboratory analyses were within normal limits before as well as after each period of treatment.

METHODOLOGICAL CONSIDERATIONS

A. Selection of patients

Allergological examination was the basis of the selection. The examination included history, ordinary ENT-examination, results from skin tests, analysis of IgE concentration in serum, counting of eosinophilic cells in nasal smear and findings at nasal provocation tests.

1. History

All patients had suffered in varying degrees from nasal stuffiness, nasal secretion, sneezing, nasal itching and eye symptoms during at least one year. Only seasonal symptoms were allowed for acceptance in the hay-fever group. In the case of perennial symptoms special attention was paid to subjective reactions at exposures to animals, dust and conceivable sources of mould.

2. ENT-examination

Anterior and posterior rhinoscopy was performed. Patients with nasal malformations, septal deformities and nasal polyps were excluded.

3. Skin test

The intracutaneous test was used in these studies as it is considered more sensitive than the prick test (Indrajana et al., 1971). Skin reactions, non-corresponding with history, were checked with nasal provocations.

4. Analysis of IgE-concentrations in serum

IgE is normally present in the serum of all individuals.

The concentration in healthy adults is usually in the order of 10-100 units/ml (20-200 ng) (Pharmacia Diagnostics AB, 1977). Patients with atopic diseases have mostly elevated concentrations of IgE in their serum (Johansson et al., 1972).

Analyses of IgE were normally not performed when allergy was established with other methods. On the other hand concentrations of IgE in serum were determined in the skin-test-negative patients classified as patients with vasomotor rhinitis as well as in normal persons.

5. Counting of eosinophilic cells in nasal smear

An eosinophilic chemotactic factor is released at reagin-mediated reactions and thought to be responsible for the accumulation of eosinophilic cells in the shock organ (cf. Plaut & Lichtenstein, 1978). An increased number of eosinophilic cells in nasal smear might indicate allergic etiology and few eosinophils may suggest non-allergic etiology of nasal symptoms (Bickmore, 1978; Malmberg & Holopainen, 1979). Even if the diagnostic value of nasal eosinophilia is questionable (Kellner et al., 1970; Mullarkey et al., 1980; Whelan, 1980) estimations of eosinophilic cells in nasal smear were carried out in studies including patients classified as suffering from vasomotor rhinitis.

6. Diagnostic nasal allergen provocations

Allergen challenge of the shock organ is the only test which provides information about the sensitivity of the shock organ to the allergen examined. Nasal provocation test was always made in cases of non-corresponding history and skin test, and furthermore in most cases of negative skin-test reaction for dust and mould.

7. Classification of subjects

a) Patients with hay fever

In all subjects described as patients with hay fever, the diagnosis was based on data positive for allergic rhinitis, i.e. hay-fever trouble during at least the last two pollen seasons, positive skin test and nasal provocation reactions.

b) Patients with vasomotor rhinitis

In subjects classified as patients with vasomotor rhinitis the diagnosis was based on a history with perennial symptoms of nasal obstruction, secretion and sneezing and on evidence of non-allergic etiology, i.e. negative skin test and nasal provocation reactions, as well as usually low concentration of IgE in serum and few eosinophilic cells in nasal smear.

c) Normal volunteers

Individuals selected as normal volunteers had never had symptoms of allergic/vasomotor rhinitis, dermatitis, urticaria or bronchial asthma and had no heredity for these diseases. Analysis of IgE/serum was within normal limits.

B. Quantitative nasal allergen provocations

1. Pollen grains or extracts for provocation

Application of crude pollen or extracts of pollen can be used for qualitative allergen challenges in hay-fever patients. At quantitative analyses of repeated challenges the use of native pollen is inexpedient as the number of pollen at each provocation test will be different in most cases (Wihl & Mygind, 1977). With pollen extract this error might be reduced when solu-

tions from the same batch are used at every provocation. In order to preserve the same activity in the extracts, the stock solution of allergen (1:10) was stored in a refrigerator throughout the experiments and new dilutions were prepared each week (Foucard et al., 1973; Center et al., 1974). These were also stored in a refrigerator until 45 min before using.

2. Forms for administration of extracts

Solutions can be administered to the nasal mucosa as nose drops from a pipette, by means of spraying equipment or discs soaked in the solution (cf. Okuda, 1977 a). As every patient with hay fever will have a response in the lower airway to inhaled allergen (cf. Norman, 1978) and variations of pulmonary resistance induce changes in nasal patency (cf. Taylor, 1973), the spraying principle was rejected. The same objection might also be made to the nose-drop technique. The disc method has a drawback by inducing nasal changes during the application (McLean et al., 1976). However, the magnitude of these is easy to evaluate and the disc method was selected for the allergen challenges.

3. Area for provocation

Nasal challenges may include only one or both nasal cavities. Natural exposure to allergens comprises bilateral provocation, but this form of challenges was excluded as repeated nasal administration of allergens involves risks of hyposensitization (Taylor & Shivalkar, 1971; Mehta & Morrison Smith, 1975; Deuschl & Johansson, 1977) or "priming effect" (Connell, 1969), i.e. a decreased or increased nasal reaction. The risk of "priming effect" is reduced with intervals of one week between the provocations. In order to minimize the con-

sequences of repeated challenges only one nasal cavity was exposed to allergen at each provocation and the interval between each challenge was at least one week.

Various parts of the allergic nasal mucosa have different reactivity to allergens and histamine. Agger nasi and the inferior turbinate show the strongest responses (Okuda, 1977 a). Because the disc is most easily applied to the inferior turbinate this was preferred.

4. Doses of allergen and duration of exposition

During in-vitro experiments the maximum histamine release from human nasal (Kaliner et al., 1973) and lung (Orange et al., 1971) tissue is obtained within 5 min after the allergen challenge. The suitable concentration of allergen solution and duration of the provocation for inducing a positive reaction (sneezing, nasal secretion as well as mucosal swelling) were titrated for each patient. Primarily a disc with 0.05 ml of an extract in the concentration of 1:1000 was applied to the nasal mucosa for 5 min. More concentrated extracts in multiples of ten (1:100 and 1:10) were needed in all patients to obtain distinct positive reactions. Most patients were provoked for 5 min but in some patients exposition for 3 min was sufficient. The same amount and concentration of allergen extract was then utilized for each volunteer at every provocation.

C. Quantitative nasal histamine provocations

The considerations regarding nasal allergen provocations (given above as B2 and B3) are also applicable to nasal histamine provocations. The disc method was again

chosen for the histamine challenges. Provocations with histamine induce slight nasal secretion and blocking when a small volume of a concentrated solution is injected in a limited area of the nasal mucosa (Okuda, 1977 b). A more pronounced nasal response is elicited with bilateral application of histamine (Okuda, 1977 a,b). Both nasal cavities were therefore challenged with discs soaked in 0.05 ml histamine (1 mg/ml) during 5 min.

D. Nasal administration of drugs

The selection of administration mode has to be based on available equipment for administration, physico-chemical properties of the drug and methodological demands.

1. Substances, type of preparation and equipment

SCG was given as a powder and insufflated into the nose by a special device. BDP was delivered as an aerosol with the equipment for pulmonary inhalation supplemented with a special nasal adaptor. Terbutaline and KWD 2131 were administered as drops from a pipette to the nasal mucosa. This mode of administration does not seem to be a drawback but rather an advantage. To judge from the distribution of drugs in a plastic cast of the human nose (Mygind & Vesterhauge, 1978), drops from a drop-bottle have a poor dispersion. However, scintigraphic comparisons of intranasally instilled Tc99 m-labelled serum albumin show a significantly higher proportion of "good" distributions with drops than with spray (Aoki & Crawley, 1976).

2. Area of treatment

Natural exposure to allergens and irritants involves both nasal cavities, and a prophylactic or therapeutic substance has to be administered to both cavities in clinical use. As one purpose of the experimental investigations was to evaluate not only local but also general side effects (reactions to absorbed quantities) of the drugs, these have to be instilled bilaterally.

3. Doses of the drugs and time interval for application

a) Disodium cromoglycate (SCG)

Ten mg SCG to each nasal cavity increase the tolerance of antigens at nasal challenge test (Engström, 1971; Taylor & Shivalkar, 1971). Therapeutic trials including patients with seasonal and perennial allergic rhinitis have been successful in relieving symptoms at dosages of 10-20 mg SCG equally distributed to both nasal cavities 3-4 times a day (cf. Brogden et al., 1974 b). Dose-response studies in patients with allergic rhinitis (Taylor & Shivalkar, 1970; Holopainen et al., 1972) show that increasing doses of SCG do not always increase the protective effect of SCG. However, the time interval between drug inhalation and antigen challenge is critical for the protection. A dose of 10 mg SCG has a prophylactic effect against antigen challenge for a period of about 6 hours (Taylor & Shivalkar, 1971). The dosage of SCG was therefore determined at 10 mg equally distributed to both nasal cavities 4 times a day in study I.

b) Beclomethasone dipropionate (BDP)

Experiences based on trials including patients with seasonal and perennial rhinitis show that daily doses of 200-400 μ g BDP decrease the nasal symptoms (cf.

Brogden et al., 1975 b). A reduction (although not a statistically significant one) of the urinary excretion of 17-ketogenic steroids was revealed at daily intranasal application of 400 µg BDP (Mygind, 1973).

Considering this and the good therapeutic results of 300 µg BDP in patients with seasonal allergic rhinitis (Löfkvist & Svensson, 1975), the daily dosage was fixed at 300 µg BDP in study II. This dose was divided into portions of 50 µg to each nasal cavity 3 times a day. General absorption of the substances was analysed by means of estimations of cortisol in plasma.

c) Terbutaline

β₂-adrenoceptor stimulants produce bronchodilation and the clinically recommended dosage of inhaled terbutaline in the treatment of bronchial asthma is 0.25-0.50 mg, not more than 8 times a day (cf. Jack et al., 1978). At severe obstructive symptoms much higher doses of terbutaline (20 mg 4 times a day) may be used but these doses are associated with troublesome side effects (Bennis & Svedmyr, 1977).

Besides the bronchodilating effect an antiallergic capacity is attributed to terbutaline. In guinea-pig lung, terbutaline is shown to inhibit anaphylactic histamine release in the same concentrations as it induces tracheorelaxation (Sörenby, 1977).

An increasing content of intracellular cyclic AMP is suggested as a mechanism behind a decreased antigen-dependent release of mediators (cf. Holroyde et al., 1977). At experimental studies on human lymphocytes and leukocytes, incubation with isoprenaline (a β-adrenoceptor stimulant) during 30 min does not increase cyclic AMP more than the same procedure during 10 min (Gillespie

et al., 1974). Also in sensitized human lung fragments it is observed that isoprenaline yielded peak increases in tissue levels of cyclic AMP 10-15 min subsequent to the introduction of the drug (Orange et al., 1971). Incubation of guinea-pig lung by terbutaline during 15 min is also reported to decrease the antigen-induced release of histamine (Sörenby, 1977).

No study has been published in which the effects on the nasal mucosa of terbutaline or its effects at nasal challenges are determined. In a pilot study (Hegardt & Svensson, 1977) on patients with allergic rhinitis, a dose of 0.5 mg terbutaline to each nasal cavity 15 min before nasal allergen challenges had shown prophylactic effect and this dose was chosen for study III and IV. In order to obtain restricted dose-response curves experiments with tenfold increased doses (5 mg to each nasal cavity) were included.

d) KWD 2131

KWD 2131 is a new β -adrenoceptor stimulant with essential antiallergic effects (Sörenby, 1977). As no study had been carried out with KWD 2131 applied to the nose, various doses had to be evaluated.

1.25 mg KWD 2131 was previously shown to have doubtful or weak antiallergic properties in asthmatic patients (Hegardt et al., 1978) and this dosage was appointed as a low dose in study III and IV. In these investigations 5 mg KWD 2131 to each nasal cavity was also used to establish a restricted dose-response curve and to make a comparison with the same amount of terbutaline. The same dose was also used in study V, and 3 times a day (5 mg x 3) in the clinical trial during the pollen season (VI). In order to preserve the isotonicity in a small volume of KWD 2131, higher doses than 5 mg to

each nasal cavity could not be included.

As for terbutaline, KWD 2131 was given 15 min before the nasal challenge (IV, V).

E. Recording of therapeutic effects and side effects

The evaluation of therapeutic effects and side effects are based on subjective as well as objective observations.

1. Subjective estimations

Each volunteer recorded the subjective opinion of the intensity of various nasal and eye symptoms on a 0-3 scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms) at points of time fixed in advance. Obvious or suspected side effects were also noted at these points.

2. Objective estimations

a) Rhinoscopy

The rhinoscopic findings (congestion of nasal mucosa and secretion) were recorded semiquantitatively on a 0-3 scale.

b) Rhinomanometry

Both anterior and posterior rhinomanometry can be used for measurements of the nasal airway resistance of one nasal cavity as well as of the total nose. Anterior rhinomanometry is often to be preferred as all individuals can be examined by this technique - about 30% of a population cannot cooperate for posterior rhinomanometric measurements.

The adaptation of the pressure catheter to the margin of the nostril by means of adhesive tape, according to Broms (1980), is reported suitable for anterior rhinomanometry. However, it does not work at nasal challenge experiments because of insufficient adherence of the tape when secretion is increased. Evaluations of one nasal cavity can also be performed by posterior rhinomanometry if the opposite cavity is in any way mechanically obstructed. Also this method was excluded as such an obstruction may influence the air flow of the cavity to be measured. Thus both nasal cavities had to be open during the measurements and examined simultaneously with posterior rhinomanometry. Only persons who could accomplish posterior rhinomanometry could therefore be included in study III, IV and V.

The nasal air flow was measured with a pneumotachograph attached to an ordinary anaesthetic mask covering the nose and mouth. The pressure difference across the nose was estimated by recording the pressure in the oropharynx through a catheter held between teeth with lips closed and placed with its open tip in the oropharynx (posterior rhinomanometry), and simultaneously recording pressure in the mask externally to the nares. Through electronic transducers pressure-flow curves were recorded X-Y-wise on an oscilloscope and then traced by an oscillotracer with a pencil by hand to a preprinted diagram (Broms, 1980). From standardized points of the pressure-flow curve, a mathematical description ad modum Broms et al. (1981 a) was obtained for each curve. From this description an angle v_2 between the curve and the flow-axis was calculated. Increasing values of angle v_2 denote higher nasal airway resistance. Angle v_2 corresponds to R_2 (resistance) according to:

$$R_2 = 5 \times \tan v_2$$

for the total nose.

c) Objective recording of side effects

Various blood and urine analyses, cultivation of bacteria and fungi in the nasopharynx, semiquantitative gradation of tremor as well as determination of pulse frequency were used for the evaluation of side effects.

F. Outcome of methodological considerations

The methodological planning before the experimental studies resulted in an expedient method for the evaluation of the antiallergic effect of drugs applied intranasally. Thus, an excellent reproducibility of the allergen (IV) as well as the histamine (V) challenges was obtained and the inconveniences of nasal hypersensitization and "priming effect" were absent. Also the combined results of the experimental (IV) and the clinical (VI) study lead to better possibilities of predicting the clinical consequences of experimental results.

GENERAL DISCUSSION

A. Effects of disodium cromoglycate (SCG) in vasomotor rhinitis

The protective effect of SCG in perennial rhinitis has been analysed in many investigations since 1972 (see Appendix 1). No other trial than study I seems to comprise only patients with vasomotor rhinitis. The absence of allergological examination and distinct patient groups or a low number of patients with vasomotor rhinitis, absence of valid information of or different doses of SCG, and disparate preparation of the drug - powder or solution - are factors which make comparisons difficult between study I and most of the trials. Only in the investigations of Mygind et al. (1972), Holopainen et al. (1975), Fagerberg & Zetterström (1975) and Wilson & Coombes (1975) was the number of patients with vasomotor rhinitis about equal with or exceeded that of patients with allergic rhinitis, and the other data were sufficient for meaningful comparison.

Analysis of data from diary cards, rhinoscopic findings, the patients' as well as the investigators' overall evaluation of the therapeutic effect in study I showed that SCG is not superior to placebo in abolishing symptoms of vasomotor rhinitis. These results are in agreement with the conclusion of Mygind et al. (1972) based on their investigation with a 2% solution of SCG. Despite some significant differences in the symptom-relieving effect between SCG and placebo, Mygind et al. stated that SCG "nasal spray is insufficient in the clinical treatment of the majority of patients with perennial rhinitis". Fagerberg & Zetterström (1975), Holopainen et al. (1975) and Wilson & Coombes (1975) observed a more favourable effect with SCG than with

placebo. Some dissimilarities between study I and the other trials may contribute as explanations of, while other differences seem to be of little consequence for, the variable symptom-relieving effect.

The study of Wilson & Coombes (1975) was timed to the hay-fever season. This time of the investigation might have seriously influenced the outcome, since hay-fever patients were included and the results were not analysed for allergic and non-allergic participants separately. The patients in study I were investigated before the hay-fever season, while some of the volunteers in the trial of Fagerberg & Zetterström (1975) had not completed the investigation until late in the pollen season. Holopainen et al. (1975) have not specified the period of treatment. Thus, the selection of the time when the studies were made may have influenced the results.

Owing to the variability of the symptoms in patients with vasomotor rhinitis long observation periods are necessary for reliable conclusions about treatment effects. The trials of Holopainen et al. (1975) and Fagerberg & Zetterström (1975) were carried out during 4 + 4 weeks, while the results of study I are based on recordings during 6 + 1 + 6 weeks. A longer time of observation and a greater number of patients in study I than in the other two investigations might be consistent with more valid results.

The separation between patients with allergic rhinitis and those with vasomotor rhinitis is based on the findings (positive and negative, respectively) at the allergological examination. Even in a selection based on a thorough examination there may be some overlapping. Thus, patients with allergic rhinitis may be included

in the groups classified as vasomotor rhinitis. Four patients out of 19, classified as vasomotor rhinitis, had positive skin test or positive RAST test in the study of Fagerberg & Zetterström (1975). Four patients out of 29 had positive skin test in the material of Holopainen et al. (1975), while all 49 patients in study I were skin-test negative. The greater number of patients with allergic rhinitis in the materials of Holopainen et al. (1975) and Fagerberg & Zetterström (1975) than in study I is another conceivable explanation of the differences in treatment effect.

Mygind et al. (1974) have reported that the effect of SCG on blocking is less than on other symptoms in patients with perennial rhinitis. The outcome of a trial including SCG may thus be dependent on the dominating symptoms. In study I as well as in the investigations of Holopainen et al. (1975) and Fagerberg & Zetterström (1975) blocking and running seem to be the predominant symptoms and no apparent differences between the trials in this respect can explain the various treatment effect.

Nor do variations in doses of pharmaceutical preparation of SCG seem to be essential for the differences in the therapeutic results. Thus, SCG was used as a dry powder and in the same dose (40 mg/day) by Fagerberg & Zetterström (1975) as in study I. The patients in the trial of Holopainen et al. (1975) received a solution of SCG and in a lower dose (30 mg/day) than the patients in study I, but with a more favourable effect on the symptoms than that observed in study I.

Marked eosinophilia in sputum (cf. Brogden et al., 1974 a) and nasal smear (Mygind et al., 1972) is associated with an increased effect of SCG in asthma and rhinitis.

Neither Fagerberg & Zetterström (1975) nor Holopainen et al. (1975) have analysed their patients in this respect, but this seems to be of minor importance for the explanation of the varying therapeutic benefits of SCG in vasomotor rhinitis, as no differences in therapeutic success were revealed between SCG and placebo in patients with a high eosinophilic count in study I.

The negative effect in general on vasomotor symptoms does not exclude a considerable relief with SCG as compared to that with placebo in single individuals. This shows that the selection of patients is one of the crucial factors for the evaluation of the therapeutic effect of SCG in vasomotor rhinitis. The thorough allergological examination of the patients in study I seems to be the basis for the general (negative) outcome of the study.

B. Effects of beclomethasone dipropionate (BDP) in vasomotor rhinitis

Intranasal BDP has uniformly been found effective in alleviating the nasal symptoms of perennial rhinitis (see Appendix 2). Favourable results are also obtained in patients with vasomotor rhinitis. The investigation of Malm & Wihl (1976) and study II are the only trials which include solely patients with vasomotor rhinitis.

The 39 patients in study II felt symptom-free or markedly improved in 74%. Analyses of data from diary cards supported the subjective overall evaluations. Significant differences between the effect of BDP and placebo were noted for the total symptom score during the second week of treatment. This is in agreement with a gradual improvement during the first 2-3 weeks in the studies of Hansen & Mygind (1974), Tarlo et al. (1977) and Sahay

et al. (1980) including patients with allergic as well as vasomotor rhinitis, but is non-corresponding with a rapid recovery within a few days in the mixed material of Holopainen et al. (1977). The difference may perhaps be explained by the varying time for the onset of effect at disparate symptoms. In study II, sneezing was most easily counteracted by BDP and reached a statistically lower level in comparison with placebo already during the first week of treatment. Such an effect was recorded in the case of nasal secretion, nasal itching and blocking after 2, 3 and 4 weeks, respectively. Also Hansen & Mygind (1974) observed an effect on sneezing and secretion after a few days of treatment. Considering this, the relative potency of BDP on different nasal symptoms is difficult to analyse in the short-term trials of different duration. Consequently, the results as regards the potency of BDP at different symptoms are often contradictory. The improvement of different symptoms with BDP throughout 12 months has been investigated in the collaborative trial from Brompton Hospital (1980). The most favourable effect was obtained for sneezing and followed by obstruction and secretion.

The therapeutic action of BDP is shown to be dependent on the daily doses of the substance. A high dose (400 μg) induced better relief of nasal symptoms than a low dose (200 μg) (Brompton Hospital, 1980). However, in the dose-response study of Malm & Wihl (1976) with 200, 400 and 800 μg BDP/day no differences in the favourable effect on nasal obstruction and sneezing could be demonstrated. An explanation of these results, contradictory to those from Brompton Hospital (1980), may be rather short treatment periods (2 weeks) with each dose and a possible "carry over" effect of the substance (Okuda & Senba, 1980).

400 µg BDP/day, equally distributed to the two nasal cavities, was the dose used by Mygind (1973) in the first trial evaluating the action of BDP at seasonal allergic rhinitis. A weak adrenal suppression with 400 µg BDP could not be excluded from Mygind's study. Therefore a lower dose (300 µg) was chosen in a corresponding trial performed by Löfkvist & Svensson (1975). With regard to the favourable local effect of this dose in hay fever the same was chosen for study II and was found beneficial. It has been observed that many patients who start medication with 400 µg BDP can reduce the dose to 300 µg/day or even lower doses with preserved action of the substance at long-term trials with mixed materials (Holopainen et al., 1977; Brompton Hospital, 1980), or in purely allergic patients (Brown et al., 1977).

Earlier attempts with nasal application of steroids have failed as general effects of the substance were also obtained at satisfactory local action. Therefore many studies have included estimates of adrenal suppression, with analyses of cortisol in plasma or serum, excretion of 17-hydroxycorticosteroids in urine and Synacthen test (see Appendix 2). The morning value of cortisol in plasma (II) did not change during treatment with 300 µg BDP/day. Corresponding results are reported by the other investigators even with higher doses than 300 µg/day in short-term studies. The plasma cortisol content was measured before the start and after 1 year's use of intranasal BDP (up to 400 µg/day - mostly 100-200) in 13 patients without significant differences (Holopainen et al., 1977). Thus, the nasal use of BDP in doses up to 300-400 µg/day seems to be without systemic effect even at long-term treatment.

The use of corticosteroids has also been associated

with increased risks of bacterial and fungal infections. Long-term treatment with BDP in cases of bronchial asthma has also proved to involve an increased risk, especially of fungal infection (Brompton Hospital, 1974; McAllen et al., 1974; Milne & Crompton, 1974). Cultures of bacteria and fungi were not included in the investigations of Gibson et al. (1974) and Hansen & Mygind (1974), but were of considerable interest and therefore performed in study II. With the use of 300 µg BDP no changes in the bacteriological or fungal flora of the nasopharynx were revealed in study II. These findings are in accordance with those of other short- or long-term studies including patients with vasomotor rhinitis (Malm & Wihl, 1976; Holopainen et al., 1977; Tarlo et al., 1977; Brompton Hospital, 1980). Bacterial infection was not enhanced, and there was no evidence of *Candida albicans* infection in a long-term investigation (1-5 years) with nasal BDP in a purely allergic material (Brown et al., 1977). Thus the nasal use of BDP in doses up to 400 µg seems not to be restricted by an increased risk of infection in the nasal cavities and the nasopharynx.

Occurrence of epistaxis or haemorrhagic secretion from the nasal cavity is reported during treatment with BDP. In study II, during 4 weeks, blood-tinged secretion was observed in one patient. Most of the episodes in long-term studies are slight (Holopainen et al., 1977; Brompton Hospital, 1980) and the incidence and intensity of these side effects correspond with that of placebo treatment (Holopainen et al., 1977; Brompton Hospital, 1980). Also other side effects, nasal irritation, sneezing initiated by spraying and so on, are reported as minor and will not restrict the therapeutic use of BDP.

Betamethasone valerate, triamcinolone acetonide, flunisolide and budesonide are other potent steroids for local use in bronchial asthma and allergic as well as vasomotor rhinitis. Intranasal flunisolide has been used in patients with perennial rhinitis. As for most of the studies including treatment with BDP, also the investigations with flunisolide in most cases cover mixed materials - i.e. patients with both allergic and vasomotor rhinitis (Schulz et al., 1978; Sy, 1979; Incaudo et al., 1980; Sahay et al., 1980). Only one investigation (Jones et al., 1979) seems to include solely patients with vasomotor rhinitis. This group-comparative study comprised only 10 patients in the flunisolide group and 9 patients in the placebo group. The restricted number of volunteers may explain why there was no improvement with flunisolide in relation to placebo. Such an explanation seems to be supported by a comparative trial of flunisolide and BDP (Sahay et al., 1980), as no significant differences were found between the actions of the two drugs in that study. Favourable therapeutic results are recently also reported in patients with vasomotor rhinitis treated with budesonide (Balle et al., 1980).

From study I it is evident that the symptoms of vasomotor rhinitis are only occasionally affected by disodium cromoglycate (SCG), while study II revealed a considerable therapeutic effect with BDP in patients with vasomotor rhinitis. These findings are recently confirmed in a comparative placebo-controlled double-blind cross-over trial of BDP and SCG in atopic and non-atopic patients with perennial rhinitis (Hillas et al., 1980).

C. Nasal and general effects of terbutaline and KWD 2131

An inhibiting effect of the immunological release of

mediators is attributed to sympathomimetic amines in various animal and human in-vitro allergological experiments (cf. Holroyde et al., 1977). Such a capacity is also found with terbutaline and KWD 2131 (Sörenby, 1977), suggesting a protective effect of these substances also at clinical allergen exposure. The effects of reduced release of mediators in the treatment of nasal allergic symptoms might be masked by nasal vascular responses of the substances. Thus, before an evaluation was made of the antiallergic action of terbutaline and KWD 2131, an examination of the effects of substances on the non-provoked nasal mucosa had to be performed.

α -adrenoceptors dominate in the nasal vascular bed. The opinions about the existence of β -adrenoceptors, based on animal experiments, differed (Hall & Jackson, 1968; Ånggård & Edwall, 1974; Malm, 1974 b) at the planning of the studies III and IV. Also studies concerning the effects of isoprenaline, a powerful stimulant of β_1 - as well as β_2 -adrenoceptors, on the human nasal mucosa were published with contradictory results (Grobler, 1966; Cohen, 1970; McLean et al., 1976), which made further investigations necessary. The use of substances with other action profiles than that of isoprenaline might provide additional knowledge about the types of receptors found in the human nasal vascular bed. Terbutaline, a conventional β_2 -adrenoceptor stimulant with minor β_1 -adrenoceptor-stimulating properties, and a new β -adrenoceptor stimulant, KWD 2131, with no preference for β_1 - or β_2 -adrenoceptors (Sörenby, 1977), seemed suitable for such a study (III).

In study III the rhinomanometric results, rhinoscopic findings and the patients' subjective evaluations after nasal application of terbutaline and KWD 2131, to both normal persons and hay-fever patients (out of season),

showed only minor variations as compared with those after administration of placebo. Significant differences between terbutaline and placebo as well as between KWD 2131 and placebo were demonstrated solely in the case of nasal airway resistance and then only occasionally after application of 5 mg of the substances to each nasal cavity. The results from study III have been confirmed in patients with vasomotor rhinitis by the absence of significant changes of nasal airway resistance at nasal application of 1 - 1.5 mg terbutaline (Broms et al., 1981 b).

Two other studies, evaluating the nasal vascular responses to another β_2 -adrenoceptor stimulant, fenoterol (Borum & Mygind, 1980; Schumacher, 1980), were also published at about the same time as study III. Despite methodological differences between these investigations themselves and between them and study III their topics are similar and a comparison will be made. All studies included asymptomatic patients with seasonal allergic rhinitis treated with β_2 -adrenoceptor stimulants, and involved the use of posterior rhinomanometry. Both Borum & Mygind (1980) and Schumacher (1980) record slight but significant increases in the nasal airway resistance, 30 and 5-15 min, respectively, after administration of fenoterol. The doses of fenoterol vary in the two studies (100; 200, 400, and 204-576 μ g, respectively) but are most comparable with the lower dose of terbutaline and KWD 2131, which showed no significant mucosal changes (III). Different forms for calculation of nasal airway resistance, different drugs as well as various number of subjects and recordings of nasal airway resistance may contribute to non-corresponding results.

Borum & Mygind (1980) and Schumacher (1980) calculated the nasal airway resistance from the pressure flow curves at a constant flow, while study III used a circle with a given radius as a standard condition. According to Broms et al. (1981 a) the later system is preferable as all rhinomanometric pressure-flow curves can be used for valid determination of nasal airway resistance. Broms et al. (1981 a) also state that data obtained from the "circle method" are usually more symmetrically distributed than those recorded at a constant pressure or flow. The nasal airway resistance data in Schumacher's investigation (1980) also point in the same direction, as the values were not normally distributed and a non-parametric test had to be used for the statistical analysis. Borum & Mygind (1980) as well as study III made use of the data with t-test, based on a normal distribution of the recordings.

Rhinomanometry reflects changes in blood content and/or oedema in the nasal mucosa. Both a vasodilatory effect and an oedema-reducing capacity are attributed to β -adrenoceptors. Different β -adrenoceptor stimulants exhibit varying potency as regards vasodilation (O'Donnell & Wanstall, 1976) as well as oedema-reducing effect (Persson et al., 1979). As for the drugs fenoterol and terbutaline, fenoterol has a more marked vasodilatory effect in the guinea-pig hind limb than terbutaline (O'Donnell & Wanstall, 1976). A similar discrepancy in relative potency between the drugs at nasal application may be a further explanation of differences in rhinomanometric results.

Not only the general action profile for a substance but also the physico-chemical properties of the drug may be essential for the effects provoked. Fenoterol is a more lipophilic substance than terbutaline and KWD 2131, a

fact which would favour the membrane passage of this substance (cf. Fingl & Woodbury, 1975). A more potent action on conceivable β -adrenoceptors might therefore be expected with fenoterol than with terbutaline and KWD 2131. Compensation for a decreased potency of a substance in relation to other substances can be obtained by an increased dose. The high dosage (5 mg to each nasal cavity) of terbutaline and KWD 2131, together with the local application of the substances, should have induced a strong stimulation on conceivable β -adrenoceptors in the nasal capacitance vessels. A few recordings spoke in favour of such a conclusion. However, the absence of significant nasal vascular responses before and after these recordings supported the concept of only few or weak β -adrenoceptors in the nasal capacitance vessels.

The general absorption of terbutaline from the nasal mucosa induced tachycardia and tremor in the experiments with 5 mg of the substance to each nasal cavity. These effects may be experienced as dangerous by the participants despite information about the symptoms before the trial. Physical and emotional stress stimulates secretion of adrenaline, a potent α - as well as β -adrenoceptor stimulant. As α -adrenoceptors are predominant in the nasal mucosa and induce vasoconstriction, circulation of adrenaline may have masked increasing nasal airway resistance subsequent to stimulation of β -adrenoceptors by terbutaline. Although it is hard to reject such a speculation in the case of terbutaline, it still seems improbable since the rhinomanometric findings with KWD 2131, despite the absence of tremor and tachycardia, correspond to those with terbutaline.

The absence or the relative absence of β -adrenoceptors in the human nasal mucosa is indicated by the limited effect on the nasal airway resistance after local appli-

cation of terbutaline (III; Broms et al., 1981 b), KWD 2131 (III) and fenoterol (Borum & Mygind, 1980; Schumacher, 1980) as well as by the absence of the participants' subjective sensations of decreased nasal patency after the same substances (III; Schumacher, 1980) and by unchanged rhinoscopic findings after nasal administration of KWD 2131 and terbutaline (III). This makes the nasal mucosa a suitable organ for testing the antiallergic properties of these substances (IV).

D. Antiallergic effect of terbutaline and KWD 2131

The immunological release of mediators is reduced by sympathomimetic amines at various animal and human in vitro experiments (cf. Holroyde et al., 1977). Two studies concerning the effect of β -adrenoceptor stimulants on nasal allergic symptoms were published at the planning of study IV. Jorde et al. (1975) reported a prophylactic effect on nasal allergic symptoms after local application of fenoterol and salbutamol, two β_2 -adrenoceptor stimulants. McLean et al. (1976) sometimes noted protection and sometimes no protection against nasal blocking at allergen provocations with isoprenaline, a β_1 - as well as a β_2 -adrenoceptor stimulant. Also the action of terbutaline was evaluated with non-corresponding effects in two unpublished investigations performed at our laboratory. At oral treatment of patients with perennial rhinitis due to house dust, there was no difference between placebo and terbutaline (5 mg three times a day) in diminishing the patients' nasal symptoms (Svensson, 1974), while nasal application of terbutaline (0.5 mg/nasal cavity) was superior to placebo in reducing nasal obstruction at experimental allergen challenges (Hegardt & Svensson, 1977). The favourable results at nasal administration of terbutaline gave reason for further studies of the antiallergic

action of terbutaline and for evaluating such an effect of KWD 2131, a new β -adrenoceptor stimulant with appreciable antianaphylactic effect (Sörenby, 1977).

Nasal airway resistance subsequent to allergen challenges decreased after pretreatment with terbutaline and KWD 2131 compared with placebo (IV). The differences between 5 mg terbutaline and placebo, 5 mg KWD 2131 and placebo, as well as 0.5 mg terbutaline and placebo were statistically significant suggesting an antiallergic effect of the substances. These results are in accordance with those of in-vitro experiments on histamine release (Sörenby, 1977; Strandberg et al., 1979), evaluations of skin test reactions (Grönneberg et al., 1980; Hegardt & Arner, 1981), and the prior pilot study using nasal application of terbutaline before nasal allergen provocation (Hegardt & Svensson, 1977). They also agree with the investigation of Jorde et al. (1975) including nasal administration with fenoterol and salbutamol prior to nasal allergen challenges, and with two recently published studies comprising fenoterol preceding allergen challenges (Borum & Mygind, 1980; Schumacher, 1980), but are partly divergent from those reported by McLean et al. (1976).

According to McLean et al. (1976) local application of isoprenaline, prior to ragweed challenges, produced a variable inhibition of the increase in nasal airway resistance or no protection at all. Methodological variations seem to account for different results. McLean et al. (1976) used a provocation technique with an expected increase of nasal airway resistance to about 200%. A weak or moderate antiallergic action might not neutralize a strong provocation reaction. In study IV with a demonstrable antiallergic effect of terbutaline and KWD 2131, the increase of nasal airway resistance was about

100-150%. Also Borum & Mygind (1980) and Schumacher (1980) tried to induce an increase of nasal airway resistance of about 100% and revealed an antiallergic effect of fenoterol.

Different action profiles for various β -adrenoceptor stimulants may be a further explanation of dissimilar antiallergic effects. As appears from studies on animal as well as on man, terbutaline and KWD 2131, despite structural similarities, have different potency as regards cardiovascular, bronchorelaxating and antiallergic properties at equal doses of the substances (Sörenby, 1977; Strandberg et al., 1979; Pegelow & Strandberg, 1980). This type of relationship exists also between other β -adrenoceptor stimulants. According to Malta & Raper (1975) and Sörenby (1977) different β -adrenoceptor stimulants have different inhibitory effects on histamine release at in-vitro provocations. Such a variation of the antiallergic action is conceivable also at in-vivo challenges and may contribute to different results.

The high doses (5 mg to each nasal cavity) of terbutaline and KWD 2131 showed equal prophylactic effect at the nasal challenges (IV). These results are in accordance with those in guinea-pig experiments (Sörenby, 1977). Also the low dose of terbutaline (0.5 mg/nasal cavity) induced a protective effect at nasal allergen provocation, while such a protection could not be demonstrated in the case of the low dose of KWD 2131 (1.25 mg) in study IV. Different slopes of the dose-response curve for terbutaline and KWD 2131 or a displacement to the right for that of KWD 2131 might provide an explanation of this divergence.

The antiallergic capacity of KWD 2131 is also assessed in patients with extrinsic asthma (Hegardt et al., 1980;

Pegelow & Strandberg, 1980). Only non-bronchodilating doses (0.25 or 0.5 mg at pulmonary inhalation and 0.3 or 0.6 mg at s.c.injection, respectively) of KWD 2131 could be examined. These doses correspond mostly with the low dose (1.25 mg to each nasal cavity) of KWD 2131 at the nasal challenges (IV). The absence of an antiallergic effect of KWD 2131 in low doses at in-vivo studies (IV; Hegardt et al., 1980; Pegelow & Strandberg, 1980) are contradictory to the promising antiallergic effect of the substance at in-vitro examinations as reported by Sörenby (1977).

Recently other studies on human tissue have revealed varying differences in antiallergic potency between KWD 2131 and terbutaline. Thus in an in-vitro study on the human lung, terbutaline was about 7 times more potent than KWD 2131 (Strandberg et al., 1979) while the corresponding figure in an in-vivo study, evaluating human skin-test reactions, was 20 (Grönneberg et al., 1980). Contradictory to this Hegardt & Arner (1981) reported an equal reduction of allergen skin-test reactions with KWD 2131 and terbutaline. Varying doses of terbutaline and KWD 2131 as well as disparate mode of application of the substances may explain the different results of the skin-test studies.

The rhinomanometric results in study IV were not supported by the patients' subjective opinion of symptom relief. The clinical value of the substances was not established and had to be evaluated in a special trial (VI).

E. Inhibition of histamine-induced effects or a mast-cell-stabilizing action of KWD 2131

The antiallergic action of terbutaline and KWD 2131 may be explained by a mast-cell-stabilizing effect (reduced

mediator release - mainly histamine) and/or an inhibition of histamine-induced effects of the substances. The inhibitory action of β -adrenoceptor stimulants on the release of histamine at allergen challenges of human (Strandberg et al., 1979) and animal (Sörenby, 1977) tissue suggests that terbutaline and KWD 2131 have a mast-cell-stabilizing capacity. A protective effect of β -adrenoceptor stimulants on histamine-provoked vascular effects is demonstrated in animal experiments (O'Donnell & Persson, 1978; Persson et al., 1978, 1979) and skin reactions in man (Jorde & Schata, 1978; Grönneberg et al., 1979) and may indicate an anti-oedematous effect of terbutaline and KWD 2131 also in the nasal mucosa.

There are methodological difficulties involved in the estimate of histamine release from mast cells at clinical allergen challenges in man. Histamine provocation of the human nasal mucosa and determinations of the inhibition of provoked effects by substances is a feasible method for evaluation of the mode of action of β -adrenoceptor stimulants. A decrease of histamine-induced effects indicates an action of KWD 2131 contrary to that of released histamine, while unchanged histamine-induced effects might be indirect evidence of a mast-cell-stabilizing property of KWD 2131.

A distinct antiallergic effect was recorded at the allergen challenges by use of 5 mg terbutaline and KWD 2131 to each nasal cavity (IV) but the general side effects of terbutaline (III, IV) excluded further experiments with this substance at least in such a dose. Only KWD 2131 was therefore evaluated at the histamine challenges in study V.

The nasal responses to histamine (rhinomanometric determinations, rhinoscopic findings and patients' sub-

jective opinions) were not affected by KWD 2131, neither in the allergic nor in the non-allergic individuals (V), suggesting a mast-cell-stabilizing capacity of the substance. These results are in accordance with those of a study evaluating the influence of KWD 2131 on histamine skin-test reactions. According to Hegardt & Arner (1981) KWD 2131 elicited a negligible reduction of histamine skin-test reactions.

As regards terbutaline, Hegardt & Arner (1981) noted no inhibition of histamine-induced skin-test reactions, while Grönneberg et al. (1979) recorded a 30% reduction (statistically significant) of wheal response but no inhibition at all of the flare reaction. Jorde & Schata (1978) reported a weak decrease of the histamine skin response with terbutaline and a more pronounced inhibition with salbutamol and fenoterol. Thus to judge from study III and V, and in accordance with the investigations on the skin, it seems reasonable to assume that the principal prophylactic effect of KWD 2131 and terbutaline at nasal allergen challenges (IV) is a mast-cell-stabilizing action with reduced release of mediators.

An increased effect on mucociliary transport is also attributed to β -adrenoceptor stimulants (Santa Cruz et al., 1974; Mossberg et al., 1977). This action might be of value in the treatment of allergic asthma and rhinitis, but is unimportant for the protective effect of KWD 2131 and terbutaline at the nasal allergen challenges in study IV with paper discs soaked in allergen and attached to a small area of the anterior part of the inferior turbinate.

F. Clinical value of KWD 2131 in allergic rhinitis

Results as regards the action of drugs from experimental

studies are not directly transferable to medical uses of the substances. The clinical relevance of experimental findings is fundamental and requires special investigations.

The antiallergic effect of 5 mg terbutaline and 5 mg KWD 2131 was distinctly established rhinomanometrically at the experimental allergen provocations in asymptomatic (out of season) patients with hay fever (IV). However, rhinoscopy and the patients' subjective opinion could not demonstrate such an effect of the substances and the clinical value of the drugs during the pollen season was of interest. The side effects after administering 5 mg terbutaline to each nasal cavity precluded further evaluations with this substance, at least in that dose. As the antiallergic effect after application of 5 mg KWD 2131 to each nasal cavity was equal with that of 5 mg terbutaline, and KWD 2131 did not exhibit any side effects, this substance was selected for a clinical trial.

The clinical study was carried out during the grass-pollen season and data on daily pollen counts were obtained. The number of grass pollen/m³ air varied during the investigation but was always enough to elicit allergic symptoms in the patients. No protective effect of 5 mg KWD 2131 to each nasal cavity three times a day could be established from diary card data and rhinoscopic findings (VI). This is in agreement with the patients' subjective opinion of symptom relief and the rhinoscopic examination of nasal mucosa at the allergen challenges (IV), but is in contrast to the results derived from the rhinomanometric measurements (IV). An explanation of this disagreement may be a higher sensitivity in rhinomanometric measurements than in rhinoscopic examinations and the patients' subjective evaluations.

After comparisons of nasal airway resistance with rhinoscopic findings in 1000 patients, McCaffrey & Kern (1979) conclude that rhinoscopic evidence of nasal deformity could not be used to predict an increase in nasal resistance. Similar restrictions are probably applicable also to rhinoscopic assessment of moderate variations in nasal mucosal swelling. Cohen (1978) reports that a reduction of the flow/resistance values by at least 15-20% gives rise to subjective symptom relief in patients with common cold. In relation to placebo, KWD 2131 reduced the nasal airway resistance by 20-30% at the allergen provocations (IV). The absence of protective effect of KWD 2131 in the clinical trial during the pollen season seems to call for higher improvement (more than 30%) of the nasal airway resistance before recommendations are made for clinical testing of a drug.

Experience of clinical treatment of allergic rhinitis with β -adrenoceptor stimulants is limited. Oral treatment of perennial rhinitis due to house dust with terbutaline showed that there is no difference between placebo and terbutaline in reducing nasal symptoms (Svensson, 1974). Recently Munro-Ford (1980) reported "some degree of improvement" of nasal allergic symptoms at local treatment with fenoterol in a corresponding trial. However, Munro-Ford (1980) seems not to have analysed the results statistically. Preliminary data from trials during the pollen season (Borum & Mygind, 1980; Schultze-Werninghaus & Gonsior, 1980) indicate a slight beneficial effect with nasal application of fenoterol in hay-fever patients.

Thus the therapeutic action of β -adrenoceptor stimulants at nasal allergic symptoms vary in different studies and the clinical value of these substances is not convincingly proved. This makes recommendations for the use of β -adrenoceptor stimulants in allergic rhinitis difficult.

SUMMARY

The effects of nasal application of disodium cromoglycate (SCG), beclomethasone dipropionate (BDP), terbutaline and KWD 2131 were investigated in clinical and experimental studies. SCG and BDP were assessed for their symptom-relieving action at clinical use in patients with vasomotor rhinitis (I, II). A corresponding evaluation was performed with KWD 2131 during the hay-fever season in patients with seasonal allergic rhinitis (VI). Terbutaline and KWD 2131 were examined for their local and general effects after pure nasal administration of the substances (III) as well as for their action at experimental nasal allergen challenges (IV) in patients with hay fever. The mode of inhibitory action of KWD 2131 was investigated by means of nasal histamine provocations (V) in patients with nasal sensitivity for grass pollen.

The volunteers were examined allergologically before the investigations and were classified as patients with allergic rhinitis or patients with vasomotor rhinitis. The classification was based on their history, the outcome of intracutaneous skin tests and qualitative nasal provocations, determinations of IgE/serum and counting of eosinophilic cells in nasal smear.

All investigations were placebo-controlled and designed for double-blind cross-over evaluations. The results were based on the patients' subjective opinions (I-VI), data from diary cards (I, II, VI), rhinoscopic findings (I-VI), registrations of pulse frequency (III, IV), observations of tremor (III, IV), determinations of nasal airway resistance (III-V), laboratory blood (I, II, VI) and urine (VI) analyses as well as cultures of bacteria (I, II) and fungi (II) from nasal secretion. The clini-

cal study with KWD 2131 during the hay-fever season (VI) included data obtained from a simultaneously performed grass-pollen count.

Forty-nine patients with vasomotor rhinitis participated during 13 weeks in the study evaluating the symptom-relieving effect of SCG (I). A total dose of 40 mg SCG/day was not superior to placebo, either in the whole material or in different subgroups of the patients. Thus an effect of SCG should not be expected in patients with vasomotor rhinitis.

The value of BDP at vasomotor rhinitis was assessed in 39 patients during a 9-week study (II). Application of 300 µg BDP/day to the nasal mucosa reduced the nasal symptoms in relation to those with placebo medication. The differences in symptom scores between treatment with BDP and placebo were statistically significant for sneezing, nasal secretion, nasal itching, blocking and total symptoms after 1, 2, 3, 4 and 2 weeks, respectively. Also the patients' preferences for the treatment periods supported a beneficial effect of BDP. The bacteriological and mycological flora of the nasopharynx as well as the level of cortisol in plasma were not changed during the period with BDP in relation to those with placebo. Thus treatment with BDP in a dose of 300 µg/day is judged advisable in patients with vasomotor rhinitis.

Local and general effects after nasal application of two doses of terbutaline and KWD 2131 were evaluated in 13 asymptomatic patients with hay fever (III). Corresponding investigations were also performed in 16 healthy controls. The low dose of the substances (0.5 mg terbutaline, 1.25 mg KWD 2131 to each nasal cavity) induced neither local mucosal changes nor general

effects at comparisons with those at treatment with placebo. Also the application of 5 mg of the substances to each nasal cavity did not induce any local alterations except increased nasal airway resistance of short duration. The limited local influence of terbutaline and KWD 2131 is considered to show that there are none, only few or weak β -adrenoceptors in the nasal mucosa, and indicated that this is a suitable structure for evaluations of a potential antiallergic effect of the drugs.

The antianaphylactic effect of the two doses of terbutaline and KWD 2131 was examined in the same 13 patients with seasonal allergic rhinitis (IV). Quantitative nasal provocations were performed with paper discs soaked in allergen solutions with an expedient reproducibility. Local pretreatment with terbutaline and KWD 2131 (5 mg to each nasal cavity) induced a significant reduction (20-30%) of the nasal airway resistance in comparison with that after treatment with placebo. No differences in the local action between 5 mg terbutaline and the same dose of KWD 2131 were demonstrated. A low dose of terbutaline (0.5 mg to each nasal cavity) reduced the nasal airway resistance at the allergen challenges, while such an effect could not be established with a low dose (1.25 mg/nasal cavity) of KWD 2131. The patients' subjective opinions and rhinoscopy did not reveal any differences in symptom-relieving effect between terbutaline, KWD 2131 and placebo. The absence of side effects with 5 mg KWD 2131 and an antiallergic effect comparable to that of terbutaline made KWD 2131 suitable for further studies (V, VI).

To clarify the mode of action of KWD 2131 nasal histamine provocations were performed with the disc method in 11 patients with seasonal allergic rhinitis (V). In

corresponding challenges 11 healthy controls also participated. The provocations were preceded by treatment with KWD 2131 and placebo. The nasal responses to histamine, based on the patients' subjective opinion, findings at rhinoscopy, the number of sneezing attacks, and rhinomanometric data, were of equal intensity independently of the type of pretreatment. The absence of protective action with KWD 2131 at the nasal histamine challenges supports a mast-cell-stabilizing ability on the part of the substance at the nasal allergen challenges.

The clinical value of 5 mg KWD 2131 to each nasal cavity three times a day was assessed during four weeks of the hay-fever season in 27 patients with nasal sensitivity to grass pollen (VI). Neither in days with high nor in days with low grass-pollen count was KWD 2131 superior to placebo in symptom-relieving ability. The absence of effect with KWD 2131 in clinical use during the hay-fever season together with the data derived from study IV shows the necessity of an improvement of nasal airway resistance exceeding 30% at experimental nasal allergen challenges before recommendations are made for clinical testing of a drug.

Appendix 1

TREATMENT WITH DISODIUM CROMOGLYCATE IN TRIALS INCLUDING ADULT PATIENTS WITH VASOMOTOR RHINITIS

Author(s)	No. of patients			Powder (P) or Solu- tion (S)	No. of doses/ day	Dose/ appli- cation	Total daily dose	Type of investi- gation	Duration of inves- tigation	Patients' pre- ferences	Diary card data			Side effects
	Total	AR	VR								Obstruction	Secretion	Sneezing	
Holopainen et al.	1972	52	26 ¹	?	P	4	20	80	DBCO	3+3 w	SCC	?	?	Nasal irritation
Mygind et al.	1972	25	13	12	S 2X	-	-	-	DBCO	4+4 w	No diff.	No diff.	Sign.	- ¹
Hopper & Dawson	1972	37	?	?	P	4	20	80	DB	4 w	SCC	Sign.	Sign.	-
Brain et al.	1974	29	28	1	S 2X	6	3.2	~20	DBCO	4+4 w	SCC	Sign.	Sign.	Nasal irritation
Mygind et al.	1974	32 ¹	?	?	S 2X	6	?	?	DB	4 w	SCC	No diff.	Sign.	- ¹
Blair & Viner	1975	19	18	1	S 2X	5-6	?	~20	DBCO	4+4 w	SCC	No diff.	Sign.	Sore throat, nasal irritation
Fagerberg & Zetterstrom	1975	23	4	19	P	4	10	40	DBCO	4+4 w	SCC	Sign.	Sign.	Nasal irritation
Girard & Bertrand	1975	30	22	8	S 2X	6	~5	~30	DB	4 w	SCC	No diff.	Sign.	- ¹
Holopainen et al.	1975	40	11	29	S 2X	6	~5	~30	DBCO	4+4 w	SCC	Sign.	Sign.	- ¹
Lobaton et al.	1975	24	14	10	S 2X	6	~5	~30	DBCO	4+4 w	SCC	Sign.	Sign.	Sore throat, nasal irritation
Wilson & Coombes	1975	38	20	18	P	4	10	40	DBCO	4+4 w	SCC	Sign.	Sign.	Sneezing, epistaxis
Balle & Illum	1977	24	?	?	S 2X	6	~5	~30	DBCO	4+4 w	SCC	Sign.	Sign.	-
Boland	1977	27	22	5	S 2X	6	~5	~30	DBCO	4+4 w	SCC	Sign.	Sign.	Nasal irritation
Loftqvist et al.	1977	49	0	49	P	4	10	40	DBCO	6+1+6 w	No diff.	No diff.	Sign.	Sore throat, nasal irritation
Morill et al.	1978	30	9	21	S 2X	?	?	?	DBCO	4+4 w	SCC	Sign.	Sign.	Nasal irritation
Sorri et al.	1979	38	27	11	S	6	?	?	DBCO	4+4 w	SCC	Sign.	Sign.	- ¹
Billas et al.	1980	52	31	21	S 2X	6	?	?	DBCO	4+4+4+4 w	SCC	?	?	-

AR = allergic rhinitis; VR = vasomotor rhinitis; DB = double-blind; DBCO = double-blind cross-over; w = weeks;

Sign. = significant reduction of the parameter with SCG; No diff. = no difference between placebo and SCG;

? = no accountability.

¹ = 16 normal persons included

TREATMENT WITH BECLOMETHASONE DIPROPIONATE (BDP) IN TRIALS INCLUDING ADULT PATIENTS WITH VASOMOTOR RHINITIS

Authors	No. of patients				Patients with		Type of investi- gation	Daily dose of BDP	Duration of treatment with BDP	Hormonal analyses	Culture of	
					Bacteria	Fungi						
	Total	AR	VR	Asthma Nasal polyps								
Gibson et al.	1974	25	16	9	20	?	DBCO	200	3 w	Cortisol/p	-	-
Hansen & Mygind	1974	21	15	6	?	?	DBCO	400	3 w	-	-	-
Morrison Smith et al.	1975	45	28	17	?	?	DBCO	400	2 w	-	-	-
Löfkvist & Svensson	1976	39	0	39	0	0	DBCO	300	4 w	Cortisol/p in 19 pat.	Incl.	Incl.
Malm & Wihl	1976	21	0	21	0	0	DBCO	$\left\{ \begin{array}{l} 200 \\ 400 \\ 800 \end{array} \right.$	$\left\{ \begin{array}{l} 2\ w \\ 2\ w \\ 2\ w \end{array} \right.$	Cortisol/s 17 OHCS/u	Incl.	Incl.
Holopainen et al.	1977	50	37	13	?	?	DBCO	400	3 w	-	Incl.	Incl.
		44	?	?	?	?	Open	400 or lower	1 year	Cortisol/p in 13 pat.	Incl.	Incl.
Lahdensuo & Hahtela	1977	27	7	20	13	Incl.	Open	400	10 days	-	-	-
Tarlo et al.	1977	25	16	9	6	8	DBCO	400	3 w	-	Incl.	Incl.
Brompton Hospital	1980	108	67	41	24	7	DB	$200\left\{ \begin{array}{l} \text{or} \\ 400\end{array} \right\}$ lower	1 year	-	Incl.	Incl.
Bunnag et al.	1980	48	44	4	7	?	Open	400	6 w	-	-	-
Hillas et al.	1980	52	31	21	Incl.	Incl.	DBCO	400	4 w	-	-	-
Sahay et al.	1980	55	51	4	Incl.	?	DB	400	4 w	Synacthen test	-	Incl.

AR = allergic rhinitis; VR = vasomotor rhinitis; DB = double-blind; DBCO = double-blind cross-over; w = weeks;
Incl. = included; - = not included; ? = no accountability.

ACKNOWLEDGEMENTS

I want to express my sincere gratitude to

Professor Carl-Magnus Eneroth, my chief, for never failing encouragement, constructive criticism and personal support.

Professor Karl-Erik Andersson for critical and constructive suggestions.

Associate Professor Thorvald Löfkvist, my teacher, for very generous and enthusiastic guidance and invaluable help throughout the investigation.

Doctor Per Broms, Ass. Professor Björn Jonson, Techn. Doctor Carl-Johan Lamm, Ass. Professor Lars Malm and Professor Claes Schaar for help in different ways.

Miss Agneta Thomson for excellent secretarial assistance.

REFERENCES

- Ahlquist, R.P. 1948. A study of the adrenotropic receptors. Am J Physiol 153: 586-600.
- Änggård, A. 1974. The effects of parasympathetic nerve stimulation on the microcirculation and secretion in the nasal mucosa of the cat. Acta Otolaryngol (Stockh) 78: 98-105.
- Änggård, A. 1979. Vasomotor rhinitis - pathophysiological aspects. Rhinology 17: 31-35.
- Änggård, A. & Edwall, L. 1974. The effects of sympathetic nerve stimulation on the tracer disappearance rate and local blood content in the nasal mucosa of the cat. Acta Otolaryngol (Stockh) 77: 131-139.
- Änggård, A. & Strandberg, K. 1981. Vascular effects of slow reacting substance (SRS) in the cat nasal mucosa and the appearance of a SRS-like principle in cat nasal secretion on nerve stimulation. Acta Physiol Scand. In press.
- Aoki, F.Y. & Crawley, J.C.W. 1976. Distribution and removal of human serum albumin-technetium 99m instilled intranasally. Br J Clin Pharmacol 3: 869-878.
- Balle, V. & Illum, P. 1977. Disodium cromoglycate nasal spray in the treatment of perennial rhinitis. Acta Otolaryngol (Stockh) 84: 287-291.
- Balle, V.H., Pedersen, U. & Engby, B. 1980. Allergic perennial and non-allergic, vasomotor rhinitis treated with budesonide nasal spray. Rhinology 18: 135-142.
- Bennis, J. & Svedmyr, N. 1977. A controlled comparison of salbutamol and terbutaline inhaled by IPPV in asthmatic patients: A dose-response study. Scand J Respir Dis (Suppl) 101: 113-117.
- Bickmore, J.T. 1978. Nasal cytology in allergy and infection. ORL Digest 40: 39-46.

- Blair, H. & Viner, A.S. 1975. A double blind trial of a 2% solution of sodium cromoglycate in perennial rhinitis. Clin Allergy 5: 139-143.
- Boland, N. 1977. Trial of 2 per cent of sodium cromoglycate (BP) in perennial rhinitis. J Irish Med Assoc 70: 333-334.
- Borum, P. & Mygind, N. 1980. Inhibition of the immediate allergic reaction in the nose by the beta-2 adreno-stimulant fenoterol. J Allergy Clin Immunol 66: 25-32.
- Brain, D.J., Singh, K.P., Trotter, C.M. & Viner, A.S. 1974. Sodium cromoglycate 2 per cent solution in perennial rhinitis: a clinical and histological study. J Laryngol Otol 88: 1001-1017.
- Brogden, R.N., Speight, T.M. & Avery, G.S. 1974 a. Sodium cromoglycate (cromolyn sodium): A review of its mode of action, pharmacology, therapeutic efficacy and use. Drugs 7: 164-282.
- Brogden, R.N., Speight, T.M. & Avery, G.S. 1974 b. Sodium cromoglycate (cromolyn sodium): II. Allergic rhinitis and other conditions. Drugs 7: 283-296.
- Brogden, R.N., Pinder, R.M., Sawyer, P.R., Speight, T.M. & Avery, G.S. 1975 a. Beclomethasone dipropionate inhaler: A review of its pharmacology, therapeutic value and adverse effects. I: Asthma. Drugs 10: 166-210.
- Brogden, R.N., Pinder, R.M., Sawyer, P.R., Speight, T.M. & Avery, G.S. 1975 b. Beclomethasone dipropionate: II: Allergic rhinitis and other conditions. Drugs 10: 211-217.
- Brompton Hospital/Medical Research Council Collaborative Trial 1974. Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol in the treatment of chronic bronchial asthma. Lancet ii: 303-307.

- Brompton Hospital/Medical Research Council Collaborative Trial 1980. Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol with a placebo in the treatment of perennial rhinitis for twelve months. Clin Allergy 10: 239-251.
- Broms, P. 1980. Rhinomanometry. Thesis, University of Lund.
- Broms, P., Jonson, B. & Lamm, C.J. 1981 a. Rhinomanometry. A system for numerical description of the nasal airway resistance. Accepted for publication in Acta Otolaryngol (Stockh).
- Broms, P., Malm, L. & Svensson, G. 1981 b. Nasal airway resistance in perennial non-allergic rhinitis. Postural variations and effects of topical application of terbutaline. To be published.
- Brown, H.M., Storey, G. & Jackson, F.A. 1977. Beclomethasone dipropionate aerosol in treatment of perennial and seasonal rhinitis: A review of five years' experience. Br J Clin Pharmacol 4: 283S-286S.
- Bunnag, C., Vipulakom, P., Pacharee, P. & Siriyananda, C. 1980. Intranasal inhalation of beclomethasone dipropionate in the treatment of perennial rhinitis in adults. Ann Allergy 44: 100-105.
- Cauna, N., Cauna, D. & Hinderer, K.H. 1972. Innervation of human nasal glands. J Neurocytol 1: 49-60.
- Center, J.G., Shuller, N. & Zeleznick, L.D. 1974. Stability of antigen E in commercially prepared ragweed pollen extracts. J Allergy Clin Immunol 54: 305-310.
- Cohen, B.M. 1970. The nasal respiratory handicap of expiratory airflow disease: The response to bronchodilator aerosols. Respiration 27: 406-416.
- Cohen, B.M. 1978. Clinical correlants of changes in nasal flow/resistance (Rn) measurements. Allergol Immunopathol (Madr) 6: 217-223.

- Connell, J.T. 1969. Quantitative intranasal pollen challenges. III. The priming effect in allergic rhinitis. J Allergy 43: 33-44.
- Deuschl, H. & Johansson, S.G.O. 1977. Hyposensitization of patients with allergic rhinitis by intranasal administration of chemically modified grass pollen allergen. A pilot study. Acta Allergol (Kbh) 32: 248-262.
- Eccles, R. & Wilson, H. 1973. A kallikrein-like substance in cat nasal secretion. Br J Pharmacol 49: 712-714.
- Engström, I. 1971. The effect of disodium cromoglycate on nasal provocation tests in children with seasonal allergic rhinitis. Acta Allergol (Kbh) 26: 101-105.
- Fagerberg, E. & Zetterström, O. 1975. A trial of disodium cromoglycate in perennial rhinitis. Acta Allergol (Kbh) 30: 63-72.
- Fingl, E. & Woodbury, D.M. 1975. General principles. In The Pharmacological Basis of Therapeutics (ed. L.S.Goodman & A.Gilman), 5th ed., pp. 1-46. Macmillan Publ. Co., Inc., New York.
- Foucard, T., Bennich, H. & Johansson, S.G.O. 1973. Studies on the stability of diluted allergen extracts using the radioallergosorbent test (RAST). Clin Allergy 3: 91-102.
- Gibson, G.J., Maberly, D.J., Lal, S., Ali, M.M. & Butler, A.G. 1974. Double-blind cross-over trial comparing intranasal beclomethasone dipropionate and placebo in perennial rhinitis. Br Med J 4: 503-504.
- Gillespie, E., Valentine, M.D. & Lichtenstein, L.M. 1974. Cyclic AMP metabolism in asthma: Studies with leukocytes and lymphocytes. J Allergy Clin Immunol 53: 27-33.

- Girard, J.P. & Bertrand, J. 1975. Study of 2% solution of sodium cromoglycate in perennial rhinitis assessed by subjective and objective parameters. Clin Allergy 5: 301-309.
- Grobler, N.J. 1966. Reactivity of the nasal respiratory mucosa (a clinical and epidemiological study). Thesis. Drukkerij van Denderen, Groningen.
- Grönneberg, R., Strandberg, K. & Hägermark, Ö. 1979. Effect of terbutaline, a β_2 -adrenergic receptor stimulating compound, on cutaneous responses to histamine, allergen, compound 48/80, and trypsin. Allergy 34: 303-309.
- Grönneberg, R., Strandberg, K. & Hägermark, Ö. 1980. Cutaneous responses to allergen after local pretreatment with beta-adrenoceptor stimulating and blocking agents. Allergy 35: 409-412.
- Hall, L.J. & Jackson, R.T. 1968. Effects of alpha and beta adrenergic agonists on nasal blood flow. Ann Otol Rhinol Laryngol 77: 1120-1130.
- Hansen, I. & Mygind, N. 1974. Local effect of intranasal beclomethasone dipropionate aerosol in perennial rhinitis. Acta Allergol (Kbh) 29: 281-287.
- Hegardt, B. & Arner, B. 1981. Inhibition of allergen-induced intracutaneous reactions by a new β -agonist, KWD 2131, and by terbutaline. Accepted for publication in Eur J Respir Dis.
- Hegardt, B., Lindholm, B., Löwhagen, O. & Svedmyr, N. 1978. Evaluation of the anti-allergic property of nebulized KWD 2131. Allergy 33: 332-333 (abstract).
- Hegardt, B., Löwhagen, O. & Svedmyr, N. 1980. Evaluation of the protective effect of a new β -agonist, KWD 2131, on allergen-induced bronchospasm. Allergy 35: 413-419.
- Hegardt, B. & Svensson, G. 1977. Unpublished data.

- Hiley, C.R., Wilson, H. & Yates, M.S. 1978. Identification of β -adrenoceptors and histamine receptors in the cat nasal vasculature. Acta Otolaryngol (Stockh) 85: 444-448.
- Hillas, J., Booth, R.J., Somerfield, S., Morton, R., Avery, J. & Wilson, J.D. 1980. A comparative trial of intra-nasal beclomethasone dipropionate and sodium cromoglycate in patients with chronic perennial rhinitis. Clin Allergy 10: 253-258.
- Holopainen, E., Malmberg, H. & Tarkiainen, E. 1977. Experiences of treating allergic rhinitis with intra-nasal beclomethasone dipropionate. Short-term trials and long-term follow-up. Acta Allergol (Kbh) 32: 263-277.
- Holopainen, E., Salo, O.P. & Backman, A. 1972. Experiences with disodium cromoglycate in treatment of seasonal and perennial allergic rhinitis. Rhinology 10: 119-126.
- Holopainen, E., Viner, T., Backman, A., Salo, O., Hannuksela, M. & Malmberg, H. 1975. Clinical trial of a two per cent solution of DSCG in perennial rhinitis. Acta Allergol (Kbh) 30: 216-226.
- Holroyde, M.C., Burka, J.F. & Eyre, P. 1977. Auto-modulation of release of pharmacological mediators of immediate (Type I) hypersensitivity. A review. Agents Actions 7: 421-430.
- Hopper, I. & Dawson, J.P. 1972. The effect of disodium cromoglycate in perennial rhinitis. J Laryngol Otol 86: 725-730.
- Incaudo, G., Schatz, M., Yamamoto, F., Mellon, M., Crepea, S. & Johnson, J.D. 1980. Intranasal flunisolide in the treatment of perennial rhinitis: Correlation with immunologic parameters. J Allergy Clin Immunol 65: 41-49.

- Indrajana, T., Spieksma, F.Th.M. & Voorhorst, R. 1971. Comparative study of the intracutaneous scratch and prick tests in allergy. Ann Allergy 29: 639-650.
- Ishii, T. 1980. The autonomic innervation of the nasal mucosa. In Advances in Allergology and Clinical Immunology (ed. A.Oehling, E.Mathov, I.Glazer & C.Arbesman), pp. 101-108. Pergamon Press, Oxford/ /New York/Toronto/Sydney/Paris/Frankfurt.
- Jack, D., Harris, D.M. & Middleton, Jr., E. 1978. Adrenergic agents. In Allergy. Principles and Practice. Vol I. (ed. E.Middleton, Jr., C.E.Reed & E.F.Ellis), pp. 404-427. The C.V.Mosby Company, Saint Louis.
- Jahnke, V. & Theopold, H.-M. 1977. Elektronenmikroskopische Befunde an der menschlichen Nasenschleimhaut bei Störungen des vegetativen Nervensystems. I. Ausschaltung des Sympathikus. Laryngol Rhinol Otol (Stuttg) 56: 144-150.
- Jahnke, V., Theopold, H.-M. & Naumann, H.H. 1977. Elektronenmikroskopische Befunde an der menschlichen Nasenschleimhaut bei Störungen des vegetativen Nervensystems. II. Ausschaltung des Parasympathikus infolge Vidianusdurchtrennung bei vasomotorischer Rhinopathie. Laryngol Rhinol Otol (Stuttg) 56: 959-968.
- Johansson, S.G.O., Bennich, H.H. & Berg, T. 1972. The clinical significance of IgE. Prog Clin Immunol 1: 157-181.
- Jones, L.M., Spector, S.L., English, G.M. & Taylor-Dawson, K. 1979. Treatment of perennial rhinitis with flunisolide corticosteroid spray. Ann Allergy 42: 139-144.
- Jorde, W., Bohlman, H.-G., Linsenmann, P. & Werdermann, K. 1975. Protektive Wirkung von beta-adrenergen Substanzen bei der allergischen Rhinitis. Med Klin 70: 1314-1316.

- Jorde, W. & Schata, M. 1978. Inhibitory effect of β -adrenergic stimulants on the histamine reaction of the human skin. II. Studies with several derivatives in regard to the dosage used and reaction depending on time. Arzneim Forsch/Drug Res 28: 850-852.
- Kaliner, M., Wasserman, S.I. & Austen, K.F. 1973. Immunologic release of chemical mediators from human nasal polyps. N Engl J Med 289: 277-281.
- Kellner, G., Ludwig, O. & Majer, E.H. 1970. Die Bedeutung der Zytodiagnostik für die Differentialdiagnose zwischen vasomotorischer und allergischer Rhinopathie. Mschr Ohrenheilk 104: 358-364.
- Lahdensuo, A. & Haahtela, T. 1977. Efficacy of intranasal beclomethasone dipropionate in patients with perennial rhinitis and asthma. Clin Allergy 7: 255-261.
- Leifer, K.N. & Wittig, H.J. 1975. The beta-2 sympathomimetic aerosols in the treatment of asthma. Ann Allergy 35: 69-80.
- Lobaton, P., Seranno, V., Rubio, N. & Gomez, D. 1975. Treatment of perennial rhinitis with 2% solution of sodium cromoglycate. Rhinology 13: 91-97.
- Löfkvist, T. & Svensson, G. 1975. An open assessment of Becotide^R (beclomethasone dipropionate) nasal spray in seasonal allergic rhinitis. Acta Allergol (Kbh) 30: 227-238.
- Malcomson, K.G. 1959. The vasomotor activities of the nasal mucous membrane. J Laryngol Otol 73: 73-98.
- Malm, L. 1974 a. Responses of resistance and capacitance vessels in feline nasal mucosa to vasoactive agents. Acta Otolaryngol (Stockh) 78: 90-97.
- Malm, L. 1974 b. β -adrenergic receptors in the vessels of the cat nasal mucosa. Acta Otolaryngol (Stockh) 78: 242-246.
- Malm, L. & Wihl, J.-Å. 1976. Intra-nasal beclomethasone dipropionate in vasomotor rhinitis. Acta Allergol (Kbh) 31: 245-253.

- Malmberg, H. & Holopainen, E. 1979. Nasal smear as a screening test for immediate-type nasal allergy. Allergy 34: 331-337.
- Malta, E. & Raper, C. 1975. β -adrenoceptors involved in inhibition of histamine release from sensitized guinea-pig lung. Eur J Pharmacol 30: 79-85.
- McAllen, M.K., Kochanowski, S.J. & Shaw, K.M. 1974. Steroid aerosols in asthma: An assessment of beta-methasone valerate and a 12-month study of patients on maintenance treatment. Br Med J 1: 171-175.
- McCaffrey, T.V. & Kern, E.B. 1979. Clinical evaluation of nasal obstruction. A study of 1,000 patients. Arch Otolaryngol 105: 542-545.
- McLean, J.A., Mathews, K.P., Ciarkowski, A.A., Brayton, P.R. & Solcmon, W.R. 1976. The effects of topical saline and isoproterenol on nasal airway resistance. J Allergy Clin Immunol 58: 563-574.
- Mehta, S.B. & Morrison Smith, J. 1975. Nasal hyposensitization and hay fever. Clin Allergy 5: 279-284.
- Mellander, S. & Johansson, B. 1968. Control of resistance, exchange, and capacitance functions in the peripheral circulation. Pharmacol Rev 20: 117-196.
- Milne, L.J.R. & Crompton, G.K. 1974. Beclomethasone dipropionate and oropharyngeal candidiasis. Br Med J 3: 797-798.
- Morris, H.G. 1978. Pharmacology of corticosteroids in asthma. In Allergy. Principles and Practice. Vol I. (ed. E.Middleton, Jr., C.E.Reed & E.F.Ellis), pp. 464-480. The C.V.Mosby Company, Saint Louis.
- Morrison Smith, J., Clegg, R.T., Cook, N. & Butler, A.G. 1975. Intranasal beclomethasone dipropionate in allergic rhinitis. Br Med J 2: 255.
- Mossberg, B., Strandberg, K. & Camner, P. 1977. Stimulatory effect of beta-adrenergic drugs on mucociliary transport. Scand J Respir Dis (Suppl) 101: 71-78.

- Mullarkey, M.F., Hill, J.S. & Webb, D.R. 1980. Allergic and nonallergic rhinitis: Their characterization with attention to the meaning of nasal eosinophilia. J Allergy Clin Immunol 65: 122-126.
- Munro-Ford, R. 1971. Treatment of various types of asthma with disodium cromoglycate (Intal): A two year appraisal. Ann Allergy 29: 8-18.
- Munro-Ford, R. 1980. Fenoterol hydrobromide (Berotec, Th 1165a) 0.1% solution in the treatment of allergic rhinitis. Ann Allergy 44: 112-115.
- Mygind, N. 1973. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. Br Med J 4: 464-466.
- Mygind, N., Hansen, I. & Balslev Jørgensen, M. 1972. Disodium cromoglycate nasal spray in adult patients with perennial rhinitis. Acta Allergol (Kbh) 27: 372-380.
- Mygind, N. & Vesterhauge, S. 1978. Aerosol distribution in the nose. Rhinology 16: 79-88.
- Mygind, N., Viner, A.S. & Jackman, N. 1974. The influence on nasal mucosa of unpreserved and preserved nasal sprays containing disodium cromoglycate. Rhinology 12: 49-54.
- Norill, B., Rebo, R. & Jackman, N. 1978. Perennial rhinitis - its causation and treatment, a trial of a new formulation of sodium cromoglycate. Rhinology 16: 139-148.
- Norman, P.S. 1978. In vivo methods of study of allergy. Skin and mucosal tests, techniques, and interpretation. In Allergy. Principles and Practice. Vol I. (ed. E. Middleton, Jr., C.E. Reed & E.F. Ellis), pp. 256-264. The C.V. Mosby Company, Saint Louis.
- O'Donnell, S.R. & Persson, C.G.A. 1978. β -adrenoceptor mediated inhibition by terbutaline of histamine effects on vascular permeability. Br J Pharmacol 62: 321-324.

- O'Donnell, S.R. & Wanstall, J.C. 1976. The contribution of extraneuronal uptake to the trachea-blood vessel selectivity of β -adrenoceptor stimulants in vitro in guinea-pigs. Br J Pharmacol 57: 369-373.
- Okuda, M. 1977 a. Basic study of nasal provocative test. First report: Side, site of the nose, size of site and allergen amount. Arch Oto-Rhino-Laryngol 214: 241-246.
- Okuda, M. 1977 b. Mechanisms in nasal allergy. Part I. ORL Digest 39: 26-33.
- Okuda, M. & Senba, O. 1980. Effects of beclomethasone dipropionate nasal spray on subjective and objective findings in perennial allergic rhinitis. Clin Oto-laryngol 5: 315-321.
- Orange, R.P., Kaliner, M.A., Laraia, P.J. & Austen, K.F. 1971. Immunological release of histamine and slow reacting substance of anaphylaxis from human lung. II. Influence of cellular levels of cyclic AMP. Fed Proc 30: 1725-1729.
- Pegelow, K.-O. & Strandberg, K. 1978. Evaluation of the anti-allergic property of a β -adrenoceptor stimulator, KWD 2131, given subcutaneously. Methodological aspects. Allergy 33: 333 (abstract).
- Pegelow, K.-O. & Strandberg, K. 1980. Evaluation of the bronchodilating and antiallergic properties of a beta-adrenoceptor stimulant, KWD 2131, in asthmatic patients. Allergy 35: 509-519.
- Persson, C.G.A., Ekman, M. & Erjefält, I. 1978. Terbutaline preventing permeability effects of histamine in the lung. Acta Pharmacol Toxicol (Kbh) 42: 395-397.
- Persson, C.G.A., Ekman, M. & Erjefält, I. 1979. Vascular anti-permeability effects of β -receptor agonists and theophylline in the lung. Acta Pharmacol Toxicol (Kbh) 44: 216-220.
- Pharmacia Diagnostics AB 1977. The clinical value of total and specific IgE determinations. Uppsala, Sweden.

- Plaut, M. & Lichtenstein, L.M. 1978. Cellular and chemical basis of the allergic inflammatory response. Component parts and control mechanisms. In Allergy. Principles and Practice. Vol I. (ed. E.Middleton, Jr., C.E.Reed & E.F.Ellis), pp. 115-138. The C.V.Mosby Company, Saint Louis.
- Poppius, H., Muittari, A., Kreus, K.-E., Korhonen, O. & Viljanen, A. 1970. Exercise asthma and disodium cromoglycate. Br Med J 4: 337-339.
- Sahay, J.N., Chatterjee, S.S. & Engler, C. 1980. A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin Allergy 10: 65-70.
- Santa Cruz, R., Landa, J., Hirsch, J. & Sackner, M.A. 1974. Tracheal mucous velocity in normal man and patients with obstructive lung disease; effects of terbutaline. Am Rev Respir Dis 109: 458-463.
- Schulz, J.I., Johnson, J.D. & Freedman, S.O. 1978. Double-blind trial comparing flunisolide and placebo for the treatment of perennial rhinitis. Clin Allergy 8: 313-320.
- Schultze-Werninghaus, G. & Gonsior, E. 1980. New aspects of beta-adrenergic therapy (fenoterol) in allergic respiratory disease. Allergol Immunopathol (Madr) 8: 291 (abstract).
- Schumacher, M.J. 1980. Effect of a β -adrenergic agonist, fenoterol, on nasal sensitivity to allergen. J Allergy Clin Immunol 66: 33-36.
- Silverman, M. & Turner-Warwick, M. 1972. Exercise induced asthma: response to disodium cromoglycate in skin-test positive and skin-test negative subjects. Clin Allergy 2: 137-142.

- Slavin, R.G. 1980. Effect of environmental and occupational agents on the lungs and its bronchial airways: Pathogenic mechanisms. In Advances in Allergology and Clinical Immunology (ed. A.Oehling, E.Mathov, I.Glazer & C.Arbesman), pp. 325-329. Pergamon Press, Oxford/ /New York/Toronto/Sydney/Paris/Frankfurt.
- Sörenby, L. 1977. Studies on the inhibition of anaphylactic histamine release from the guinea-pig lung by β -adrenoceptor stimulants. Thesis, Uppsala University.
- Sorri, M., Jokinen, K. & Palva, A. 1979. Disodium cromoglycate therapy in perennial rhinitis. Acta Otolaryngol (Stockh) Suppl 360: 30-32.
- Strandberg, K., Pegelow, K.-O., Persson, C.G.A. & Sörenby, L. 1979. Anti-anaphylactic and bronchodilating action of a beta-adrenoceptor stimulator, KWD 2131, in human lung tissue. Allergy 34: 221-224.
- Svensson, G. 1974. Unpublished data.
- Sy, R.K. 1979. Flunisolide intranasal spray in the treatment of perennial rhinitis. Arch Otolaryngol 105: 649-653.
- Tarlo, S.M., Cockcroft, D.W., Dolovich, J. & Hargreave, F.E. 1977. Beclomethasone dipropionate aerosol in perennial rhinitis. J Allergy Clin Immunol 59: 232-236.
- Taylor, G. & Shivalkar, P.R. 1970. The effect of disodium cromoglycate on nasal airways resistance following antigen challenge in sensitive subjects. In Disodium Cromoglycate. Papers presented at the 7th international congress of allergology, special sectional meetings. Florence, October 17th, 1970, pp. 13-19. C.E.P.I., Rome.
- Taylor, G. & Shivalkar, P.R. 1971. Disodium cromoglycate: laboratory studies and clinical trial in allergic rhinitis. Clin Allergy 1: 189-198.
- Taylor, M. 1973. The nasal vasomotor reaction. Otolaryngol Clin North Am 6: 645-654.

- Uddman, R., Alumets, J., Densert, O., Håkanson, R. & Sundler, F. 1978. Occurrence and distribution of VIP nerves in the nasal mucosa and tracheobronchial wall. Acta Otolaryngol (Stockh) 86: 443-448.
- Whelan, C.F.A. 1980. Problems in the examination of nasal smears in allergic rhinitis. J Laryngol Otol 94: 399-404.
- Wihl, J.-Å. & Mygind, N. 1977. Studies on the allergen-challenged human nasal mucosa. Acta Otolaryngol (Stockh) 84: 281-286.
- Wilson, I.I. & Coombes, J.A. 1975. Rynacrom (sodium cromoglycate) in intractable perennial rhinitis. N Zeal Med J 82: 265-266.
- Zuskin, E. & Bouhuys, A. 1974. Acute airway responses to hair-spray preparations. N Engl J Med 290: 660-663.

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TREATMENT OF VASOMOTOR RHINITIS* WITH INTRANASAL DISODIUM CROMOGLYATE (SCG)

Results from a Double-Blind Cross-Over Study

By

THORVALD LÖFKVIST, HANS RUNCRAANTZ & GUNNAR SVENSSON

The role of disodium cromoglycate (Intal®, Lomudal®) in the prophylactic management of bronchial asthma has now been firmly established for several years (2). In the upper airways, the efficacy of the drug in seasonal allergic rhinitis (hay fever) has been demonstrated both as a dry powder and a 2 per cent aqueous solution (2). Trials with the drug have also shown a considerable degree of success in patients suffering from perennial rhinitis in whom allergic factors have been demonstrable. So far, however, no studies to our knowledge, have been done solely in patients with perennial rhinitis in whom allergy has *not* been demonstrated, i.e. patients with vasomotor rhinitis. Considering the refractoriness of this condition to various therapies, and with the beneficial effect of disodium cromoglycate in asthma bronchiale of non-allergic aetiology in mind (9), we felt a trial of this drug in vasomotor rhinitis would be of interest.

* In this article the term *vasomotor rhinitis* is used in agreement with the definition of Hansel (5), i.e. symptoms simulating allergic rhinitis but with negative findings in allergological examinations.

MATERIAL AND METHODS

The study comprised 49 patients aged 16-65 years (average 34 years) with vasomotor rhinitis for many years. The symptoms were of a perennial type with varying degrees of obstruction, running, sneezing and nasal itching. Allergological examination in the form of intracutaneous tests with different extracts (six dust, two mould, eight animal epithelium and ten pollen extracts) proved negative. Pretreatment analysis of IgE/serum with RIST and estimates of eosinophils in nasal secretion, according to the classification of Koch (7), were carried out (cf. Table 1). Patients with nasal polyposis, obvious septum deviation and bronchial asthma were excluded.

TABLE 1
Pretreatment Analysis of IgE/Serum with RIST, and Estimates of Eosinophils in Nasal Secretion in 49 Patients with Vasomotor Rhinitis.*

Eosinophils	IgE/serum ng/ml					
	<100	100-200	201-300	301-400	401-500	>500
0	12	1				1 (760)
±		1				
+	7	2				
++	3	2		1 (380)		
+++	8	2				
++++	4	2				1 (520)

* IgE is lacking in two subjects with no eosinophils.

The trial was a double-blind cross-over and took place for 13 weeks during January-April 1973. Twenty-four patients started with a 6-week treatment period with SCG followed by 1 week without medication and finished with 6 weeks' placebo treatment. The other 25 patients were treated in reverse order.

SCG and placebo were presented in identical gelatin capsules and were administered as nasal powder. A specially designed insufflator was used for this. The dosage during the SCG period was 10 mg of disodium cromoglycate plus 10 mg lactose, equally distributed in both nostrils four times a day, i.e. total dose of 40 mg SCG in 24 h. The placebo capsule contained 20 mg lactose. Each subject recorded on a daily diary card the following symptoms: blocking, running, sneezing and itching on a scale 0-3 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) during all 13 weeks.

Each patient was interviewed and medically examined before entry into the trial and on the last day both in the SCG and the placebo period. The condition of the nose was recorded as to the severity of redness, oedema and purulent discharge, on a 0-3 scale as above. Haematological analysis (haemoglobin, leuco-

cyte count, differential leucocyte count and sedimentation rate) and bacteriological examination (ordinary cultivation) of the naso-pharyngeal secretion were also carried out on these occasions.

On the last day of both treatment periods, the patient's subjective evaluation of the therapeutic effect was recorded as follows: no symptoms, improved, unchanged, deteriorated, and at the last examination, their opinion as to which of the treatment periods had been most effective in controlling nasal symptoms, or whether no difference existed. The data obtained from the diary cards and medical examinations were subjected to statistical analysis.

RESULTS

In all, 49 cases were entered into the study, but full data were not obtained in all cases. The results for each treatment, based on subjective evaluation, are given in Table 2. It is apparent that the results differed little. As far as patients' preferences are concerned, the figures are shown in Table 3. Again there is no statistical evidence of any advantage in either form of treatment. This is in agreement with the findings at physical examination, in which the condition of the nasal mucosa was found unchanged in relation to treatment.

TABLE 2
Condition After Each Treatment.

Patient group	Condition	Treatment	
		SCG	Placebo
SCG-Placebo	Symptom-free	1	1
	Improved	11	9
	Not improved	10	9
	Deteriorated	1	3
Placebo-SCG	Symptom-free	0	3
	Improved	12	9
	Not improved	8	10
	Deteriorated	4	1

The summary of diary card data is given in Table 4. Analysis on the whole material and the subgroups "blockers",

“runners”, “blockers and runners”, “patients with sneezing and itching” and “patients with high eosinophilic count in nasal smear” gave no significant differences between the two types of treatment independent of drug order. Nevertheless, some patients experienced the same degree of relief with both forms of medication, or had a preference for SCG. In order to exemplify this the following cases are chosen:

TABLE 3
Patients' Preferences.

Patient group	Preference		
	SCG	Placebo	Neither
SCG-Placebo	9	9	3
Placebo-SCG	9	10	5
Total	18	19	8

TABLE 4
Summary of Diary Card Data.

Variable	Group size	Average scores for		Wilcoxon T-value*	Significance
		SCG	Placebo		
Blocking	43	46.4 $\pm$ 40.6	51.4 $\pm$ 38.9	343.0 (38)	$P > 0.10$
Running	43	46.1 $\pm$ 27.8	47.7 $\pm$ 25.9	439.5 (43)	$P > 0.10$
Sneezing	44	36.2 $\pm$ 23.1	38.5 $\pm$ 21.5	471.0 (44)	$P > 0.10$
Itching	42	22.2 $\pm$ 22.7	21.9 $\pm$ 21.4	297.0 (35)	$P > 0.10$

* Figures in brackets are the number of non-tied pairs included in the test; tied pairs are excluded.

E.F. A 22-year-old woman whose main symptoms were blocking and sneezing with some degree of running and itching. She had had symptoms for 5 years. The nasal mucosa was livid and oedematous at every examination. Before the start of treatment there were (+) eosinophilic cells in the nasal secretion. The serum IgE was 170 ng/ml. Previous treatment with antihistamines, cortisone injections and bacterial vaccine had had no effect.

After treatment with SCG no definite effect was seen against running, itching and sneezing, but for the main symptom, blocking, there was considerable im-

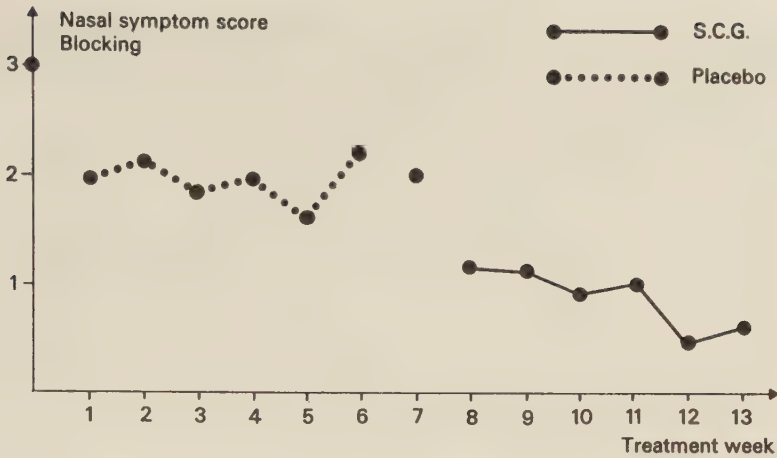


Fig. 1.

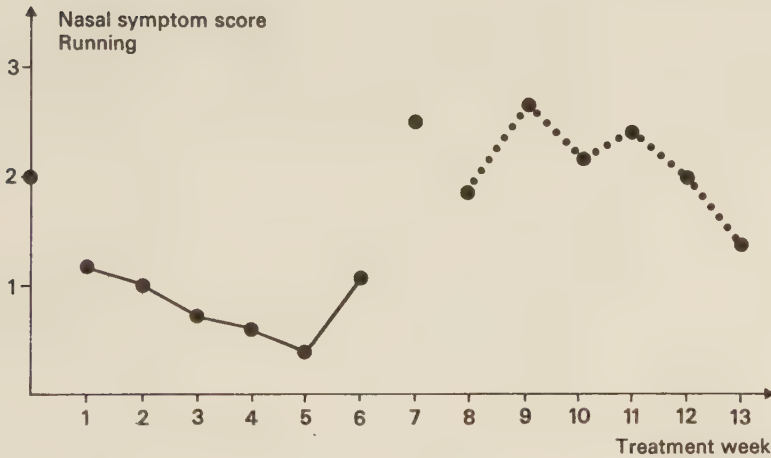


Fig. 2.

Figs. 1 and 2.

Nasal symptom score for two different patients, noted at start, once a week during the treatment with SCG and placebo and the wash-out week in between.

provement (Fig. 1). Placebo had in this respect considerably less (or no) effect and the patient preferred SCG.

I.H. A 31-year-old woman with nasal symptoms for 10 years. The main symptom was running, with the other symptoms to a lesser degree. On examination,

before starting the treatment, oedema and red nasal mucosa and (+++) eosinophilic cells in the nasal secretion were recorded. IgE/serum was 156 ng/ml. Treatment with antihistamine earlier had been without effect, while injections with bacterial vaccines had given some improvement.

In this trial SCG had the best effect on the main symptom, "running" (Fig. 2), but also some effect on blocking and itching. The effect of placebo was considered less pronounced and the patient preferred SCG.

G.I. A 26-year-old man, whose main symptoms were blocking and running for many years. On examination, before start of treatment, livid and oedematous nasal mucosa were recorded and (+++) eosinophilic cells in the nasal secretion. IgE/serum was 20 ng/ml.

SCG had no effect on running, but blocking was improved. Symptoms were unchanged during the placebo period and he preferred SCG.

Safety and Side Effects

No bacteriological changes in the nasopharynx were recorded. The haematological analysis also remained normal during both treatment periods. Side effects were reported by nine patients, five on active and four on placebo, and consisted of a feeling of dryness and irritation in the nose and throat.

DISCUSSION

As a condition of obscure aetiology, vasomotor rhinitis has been treated in many different ways, i.e. with drugs, vaccines and surgery (11) and the benefits of these treatments have not always been convincing.

No trial, on the effect of SCG in patients with vasomotor rhinitis alone, had been published when we started our study in the beginning of 1973. A great number of studies, however, were published during 1972-75 on the effect of SCG in perennial rhinitis. In these studies both allergic and vasomotor rhinitis were included. Only in a few studies is it possible to make comparisons with our own trial, as the distinction between allergic and vasomotor rhinitis was poor and the treatment periods throughout were shorter. Our patients were treated for 6 weeks with each preparation with an interval of 1 week. This rather long period of treatment was chosen in view of

the well-known variability of the symptoms of vasomotor rhinitis.

In our study of 49 patients with vasomotor rhinitis, no definite effect from SCG was seen. This result, made on statistical analysis of data concerning subjective parameters and evaluation of the status of the nasal mucosa by physical examination, conforms with that of Mygind et al. (10) in their investigation of 12 patients with vasomotor rhinitis. However, it differs from the results of Fagerberg & Zetterström (4) who studied 23 patients, of which 19 were considered suffering from vasomotor rhinitis. They found a good response to SCG and a clear preference for this drug in comparison with placebo. This was especially the case when the SCG period succeeded the placebo period. When the patients started with SCG, the difference in results was less pronounced, which was supposed to be a consequence of the long-lasting carry-over effect of the active drug, possibly due to the absence of a wash-out period.

Bernstein et al. (1) have argued that SCG could have a carry-over effect for up to 4 weeks. Like Fagerberg & Zetterström (4) we doubt this with regard to "the current opinion of the mode of action of SCG". With the method used by us—longer-treatment period plus wash-out period—the risk for carry-over effect should be reduced. As we moreover had a larger patient material at our disposal, it seems as if our results could have a greater validity.

Holopainen et al. (6) presented in 1975 a trial including 29 patients with vasomotor rhinitis and 11 patients with allergic rhinitis. The authors put together the treatment results for both these patient categories and concluded that "there is no difference in the degree of the response to SCG between intrinsic and extrinsic forms of rhinitis". Our experiences from treatment of an allergic material (8) and results from our existing trial of vasomotor rhinitis, are not in agreement with Holopainen's. Our examination of the allergic clientele showed a more favourable response to SCG. It is true that Holopainen used SCG in a 2 per cent solution while we, in this study of

vasomotor rhinitis, used powder, but we assume that the most probable explanation for the difference in treatment results for Holopainen and us is that Holopainen's patient material comprised more allergic patients than were detected. Bruun (3) has shown that among patients, characterized as vasomotor patients, allergic patients are included, in whom it is very difficult to prove allergy. One may in this connection speculate about Type I and/or Type III reactions initiated by allergens unavailable in ordinary allergological diagnosis of today. A further illustration of the difficulty of diagnosing an allergic condition is shown by our investigation. In spite of the fact that our study has not shown statistical evidence for the therapeutic effect of SCG in vasomotor rhinitis, we could see a dramatic improvement in the symptoms in some patients after treatment with SCG. These patients continued with the drug with good results. We therefore think that SCG is worth trying in cases of vasomotor rhinitis as the drug is completely atoxic (2) and its use, on the whole, is without side effects.

SUMMARY

The effect of SCG powder (Lomudal®, Intal®) intranasally in vasomotor rhinitis has been studied on 49 adult volunteers in a double-blind cross-over study during 13 weeks in January–April 1973. The dose of SCG was 40 mg/day. Although a substantial number of results were obtained, no significant difference between the effects of SCG and placebo treatment, on variables measured, was detected. However, some patients experienced relief with, and preferred, the treatment with SCG. The results from this investigation are discussed in comparison with those from other studies including patients with vasomotor rhinitis.

ACKNOWLEDGEMENTS

We wish to thank Fisons AB, Sweden, for providing the equipment used in this trial, and Dr J. Pearson and Dr A. Edwards (Medical Advisors, Fisons Research and Development Laboratories) for their assistance.

REFERENCES

1. Bernstein, L., Siegel, S. C., Brandon, M. L., Brown, E. B., Evans, R. R., Feinberg, A. R., Friedlaender, S., Krumholz, R. A., Hadley, R. A., Handelsman, N. I., Thurston, D. & Yamate, M. (1972): A controlled study of cromolyn sodium sponsored by the Drug Committee of the American Academy of Allergy. *J. Allergy clin. Immunol.* 50, 235-245.
2. Brogden, R. N., Speight, T. M. & Avery, G. S. (1974): Sodium cromoglycate (cromolyn sodium): A review of its mode of action, pharmacology, therapeutic efficacy and use. *Drugs* 7, 164-296.
3. Bruun, E. (1955): Allergic examination and anti-allergic treatment of vasomotor rhinitis. *Acta allergol.* 8, 256-264.
4. Fagerberg, E. & Zetterström, O. (1975): A trial of disodium cromoglycate in perennial rhinitis. *Acta allergol.* 30, 63-72.
5. Hansel, F. K. (1953): Clinical allergy. The C. V. Mosby Company, St Louis.
6. Holopainen, E., Viner, T., Backman, A., Salo, O., Hannuksela, M. & Malmberg, H. (1975): Clinical trial of two per cent solution of D.S.C.G. in perennial rhinitis. *Acta allergol.* 30, 216-226.
7. Koch, H. (1947): Allergical investigations of chronic otitis. *Acta oto-laryng.* (Stockh.), Suppl. LXII, p. 51.
8. Löfkvist, T. & Svensson, G. (1975): An open assessment of Lomudal® (Disodium cromoglycate) (2 per cent) nasal spray in seasonal allergic rhinitis. *Acta allergol.* 30, 89-95.
9. Munro-Ford, R. (1971): Treatment of various types of asthma with disodium cromoglycate (Intal): A two-year appraisal. *Ann. Allergy* 20, 8-18.
10. Mygind, N., Hansen, I. & Jørgensen, M. B. (1972): Disodium cromoglycate nasal spray in adult patients with perennial rhinitis. *Acta allergol.* 27, 372-380.
11. Sheldon & Lovell-Mathews (1967): A manual of clinical allergy, p. 83-86. W. B. Saunders Company, Philadelphia and London.

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By

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Local cortisone therapy with beclomethasone dipropionate must to-day be considered an established alternative in the treatment of bronchial asthma. Good therapeutic results have also been achieved in cases of hay fever, perennial rhinitis and nasal polyposis. Among the test subjects with perennial rhinitis, both allergic persons and those without evidence of allergy have been included, that is to say patients with vasomotor rhinitis*. This last group has been rather small in number. We have considered it important to test this preparation on a larger number of patients with this pathological condition than has been done earlier, using the comparatively low dosage which, according to a previous investigation, we have found to be effective against hay fever.

MATERIAL AND METHODS

The study comprised 39 patients (19 males and 20 females) aged 19-66 years (average 39 years) with a history of vasomotor rhinitis for many years. Half of

* The term vasomotor rhinitis has been assigned to those conditions characterized symptomatically by sneezing, obstruction, stuffiness, increased discharge, postnasal drip, and pathologically by the appearance of a boggy, swollen, red, sometimes pale, mucosa and where nasal allergy is excluded, (Hansel 1953 (8)).

the patients had had symptoms for more than 10 years. Their trouble was of a perennial nature in the form of obstruction, nasal drip, sneezing and nasal itching in varying degrees. Allergologic testing in the form of intracutaneous tests with 26 common extracts (6 dust extracts, 2 mould extracts, 8 animal epithelium extracts, and 10 pollen extracts) proved negative. Analysis of IgE/serum (Phadebas® IgE Test) showed the following values: < 100 ng/ml for 21 subjects, 101–200 for eight, 201–300 for four, 301–400 for two, 440, 600, 840 and 1,200 ng/ml for one patient. Estimate of eosinophilic cells in nasal secretion (7) prior to treatment showed few or fairly many eosinophils without clusters, < 10 per cent, corresponding to ($\pm$) or (+) according to Koch (10). Patients with nasal polypsis, obvious septum deviation, and bronchial asthma were not included in the material. The study originally comprised 41 patients, but two of them withdrew in the first test period owing to a suspected pregnancy and an influenza-like disease.

The study was of a double-blind cross-over type, and was continued for 9 weeks during February–April 1975. Nineteen patients started with a 4-week treatment period with beclomethasone dipropionate, followed by 1 week without medication, and finished with 4 weeks' placebo treatment. The other 20 patients were treated in the reverse order.

Beclomethasone dipropionate and placebo were distributed in identically equal packings, and were administered as a nasal spray. The beclomethasone dipropionate aerosol was the same as used for bronchial asthma, and so was the packing, apart from a special nasal adapter.

The dosage was one puff into each nostril 3 times daily both during the placebo period and during the beclomethasone dipropionate period. One puff of the active aerosol corresponds to 50 μ g of beclomethasone dipropionate, which means a total dose of 300 μ g in a 24-hour period.

Each subject recorded on a daily diary card the following symptoms: Blocking, running, sneezing and itching, on a scale 0–3 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) during all 9 weeks.

Each patient was interviewed and medically examined before entry into the trial and on the last day of both the beclomethasone dipropionate and the placebo period. The condition of the nose was recorded as to the presence of lividity, redness, oedema, and purulent discharge, again on a 0–3 scale as above. Haematological analysis and bacteriological examination of the nasopharyngeal secretion were also carried out on these occasions. Estimation of cortisol/plasma (modification of the method of De Moor et al. (4, 5)) was made in 19 patients at 8 a.m. once during the last week of the placebo period and once during the beclomethasone dipropionate treatment period.

On the last day of both treatment periods, the patients' subjective evaluation of the therapeutic effect was recorded as follows: No trouble, improved, unchanged, worsened, and at the last examination, their opinion as to which of the treatment periods had given the least nasal trouble, or whether they had found no difference between the two periods.

Statistical Methods

The data obtained from the diary cards and medical examinations were subjected to statistical analysis.

"A linear nonparametric permutation test for matched pairs" was used, estimating the decreases of nasal score during the two respective periods.

Comparison between the period of beclomethasone dipropionate and the placebo period was carried out in the following way: One group (A) was treated with placebo in the first period and with beclomethasone dipropionate in the second period. The other group (B) started with beclomethasone dipropionate and afterwards received placebo. The difference in nasal score between the first and the second period was determined for each patient in both groups. These differences for group A were compared with the corresponding differences for group B using Fisher's permutation test, which is a nonparametric test.

RESULTS

Twenty-five patients out of the 39 who accomplished the investigation preferred the beclomethasone dipropionate period, whilst five patients preferred the placebo period, and nine did not find any difference between the periods.

On questioning after the beclomethasone dipropionate period, four patients considered themselves free of trouble, 25 had improved, 10 were unchanged, and no one had worsened during the period, whereas after the placebo period no one was free of trouble, 12 had improved, 20 were unchanged, and seven patients had worsened.

An investigation as to whether the trouble score decreased in either the placebo period or the beclomethasone dipropionate period, showed no significant decrease for any variable during the entire placebo period. On the other hand, a significant reduction of the trouble score for all symptoms as well as total nose score (the total of the four single symptoms) between day 1 and the average for week 1 were registered during the beclomethasone dipropionate period. This effect was sustained throughout the period of treatment.

Table 1 shows the result of a comparison of the trouble score during the respective periods, i.e. corrected for placebo effect. For the different nasal symptoms the result deviated to some extent from the one shown above, since only the

TABLE 1

Comparative Statistical Analysis of the Results from Diary Cards During the Periods of Treatment with Beclomethasone Dipropionate and Placebo. The Significant P-Values Favour Treatment with Beclomethasone Dipropionate.

Sneezing	Day 1	n.s.
	Week 1	$P < 0.05$
	Week 2	$P < 0.01$
	Week 3	$P < 0.01$
	Week 4	$P < 0.01$
Nasal catarrh	Day 1	n.s.
	Week 1	n.s.
	Week 2	$P < 0.01$
	Week 3	$P < 0.01$
	Week 4	$P < 0.01$
Itching	Day 1	n.s.
	Week 1	n.s.
	Week 2	n.s.
	Week 3	$P < 0.05$
	Week 4	$P < 0.05$
Blocking	Day 1	n.s.
	Week 1	n.s.
	Week 2	n.s.
	Week 3	n.s.
	Week 4	$P < 0.01$
Total score	Day 1	n.s.
	Week 1	n.s.
	Week 2	$P < 0.01$
	Week 3	$P < 0.01$
	Week 4	$P < 0.01$

n.s. = not significant.

therapeutic result recorded for each particular preparation was considered. Thus it was only during the second week that a significantly lower total score during the beclomethasone dipropionate treatment was observed. This effect remained throughout the rest of the period. For the individual nasal symptoms a significantly lower trouble score for the beclomethasone dipropionate period was registered as follows: for

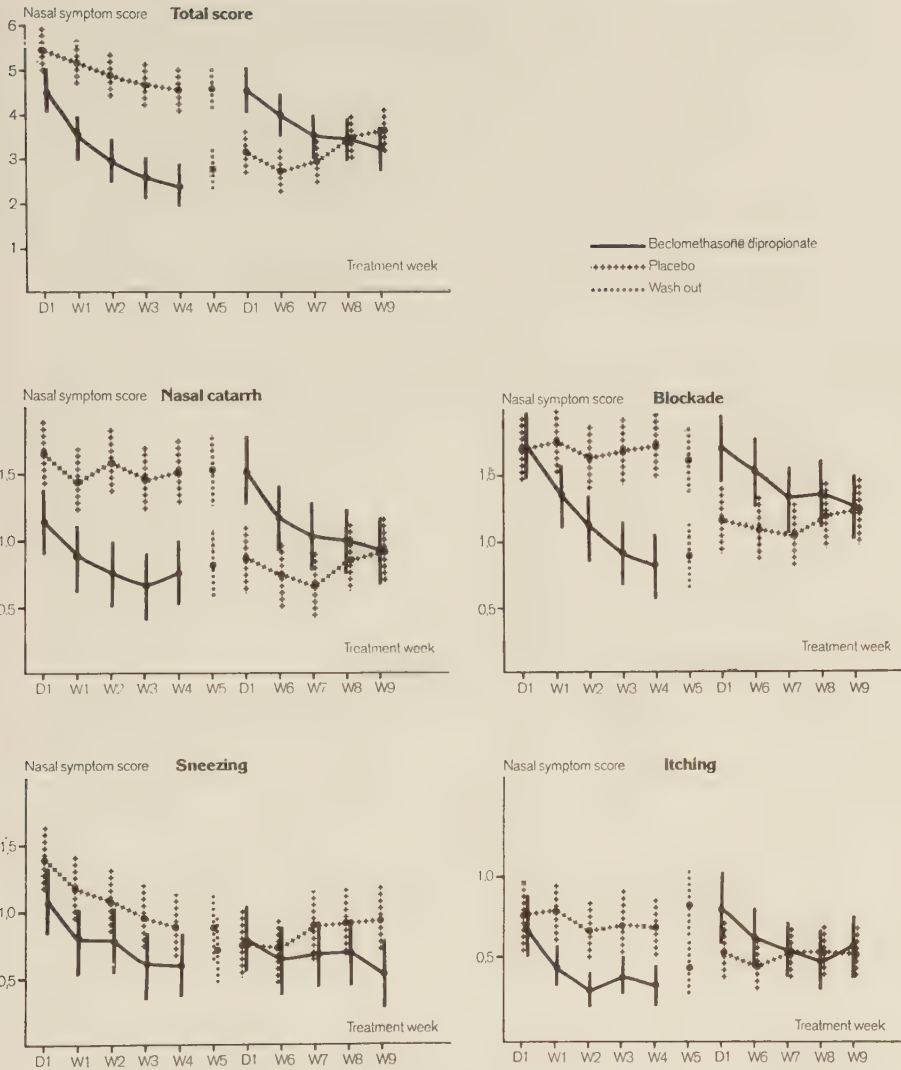


Fig. 1.

Average daily total nasal score and daily score for nasal catarrh, blockade, sneezing and itching from diary cards in 39 patients with vasomotor rhinitis treated with beclomethasone dipropionate and placebo for 4 weeks respectively. One week's wash-out period separates the two treatment periods. Data noted the first day (D₁) of both treatment periods and once a week (W₁–W₉).

TABLE 2

Estimations of Morning Plasma Cortisol Level During the 4th Week of Treatment with Beclomethasone Dipropionate and Placebo in 19 Patients with Vasomotor Rhinitis.

Patient	Born	Sex	Cortisol level during	
			Beclomethasone dipropionate period ($\mu\text{g}/100\text{ ml}$)	Placebo period ($\mu\text{g}/100\text{ ml}$)
I.O.	1942	male	14	18
M.S.	1920	female	19	20
J.T.	1951	male	14	22
E.B.	1946	female	16	16
M.O.	1917	female	20	32
E.B.*	1953	female	29	38
B.S.	1926	male	12	12
A.T.	1946	female	20	18
G.H.	1909	male	16	20
C.F.	1937	male	19	17
B.N.	1923	female	14	19
A.O.	1931	female	17	20
I.F.	1948	male	27	20
C.S.	1952	female	19	15
I.A.	1923	female	23	19
G.S.	1947	male	32	27
L.W.*	1956	female	41	47
E.O.*	1953	female	44	53
B.P.	1946	female	18	18
Average			21.8	23.7

Normal level of plasma cortisol 8 a.m.: 10-30 $\mu\text{g}/100\text{ ml}$.

* Patient using contraceptive pills.

sneezing already during the first week, for nasal catarrh during the second week, for nasal itching during the third week, and for nasal blocking only during the fourth week of treatment.

Fig. 1 illustrates graphically the total score and the score for each nasal symptom during treatment with beclomethasone dipropionate, placebo, and the wash-out period in between.

The rhinoscopic examination showed there had been no therapeutic effect for lividity, redness, oedema, and purulent secretion.

Cultures for bacteria and *Candida albicans* from the nasopharynx were generally negative. Thus the analysis was negative for *Candida albicans* in all patients on all three test occasions. Furthermore, no pathogenic bacteria could be isolated on any test occasion in 31 patients. In four patients new bacteria growth was found after the beclomethasone treatment, whereas two patients with bacteria growth before the beclomethasone treatment were free from bacteria at the end of the period of treatment. After the placebo period, fresh growth was isolated in two patients. Diagnosed pathogenic types of bacteria were *Haemophilus influenzae*, *Neisseria catarrhalis*, plasma-coagulating staphylococci, and beta haemolytic streptococci.

The mean cortisol/plasma value was somewhat lower during the beclomethasone dipropionate period than during the placebo period, but this difference is not statistically significant. For the individual patients, definite pathological values were observed only in the three women taking contraceptive pills. For the rest, two patients were noted to have slightly elevated values, one of which was found in the beclomethasone period and the other in the placebo period. (Cf. Table 2).

No serious side effects have been observed. One patient had a blood-tinged secretion from the nose towards the end of the beclomethasone period. No certain source of bleeding was ascertained. The trouble disappeared in the medicine-free week and did not recur during the placebo period following. One patient withdrew on account of an influenza-simulating disease during the beclomethasone treatment period. A few patients experienced increased irritation from itching, sneezing, nasal catarrh, and blocking following spraying with placebo as well as beclomethasone dipropionate.

DISCUSSION

Vasomotor rhinitis is, in many respects, an aetiologically obscure pathological condition. For this reason it has become the object of a wide range of therapeutic measures, such as treatment with drugs, vaccines, and surgery (17). Corticosteroids, for oral or parenteral use, will usually relieve the symptoms (2).

The synthesis of high-grade locally active corticosteroids has opened the possibility of a successful local cortisone therapy with reduced risk of systemic hormonal side effects. Good results with beclomethasone dipropionate in varying dosages have been shown in seasonal allergic rhinitis (1, 11, 15), perennial rhinitis (6, 9, 14), and nasal polyposis (16). As a natural extension of our investigation of hay fever (11) we continued with a study of vasomotor rhinitis treated with the same dose of beclomethasone (300 μ g a day) that had proved successful in the previous trial.

The study had the character of a double-blind cross-over study, allowing an evaluation of the therapeutic effect in 39 adult patients with vasomotor rhinitis without polyposis, which is, as far as we know, the greatest number of patients with this pathological condition that has been evaluated in a special investigation.

The results must be considered encouraging. About three-quarters (74 per cent) of the patients considered themselves to be free of trouble or improved when treated with beclomethasone dipropionate. The subjective evaluation corresponded with the results obtained at the statistical processing of the trouble score. The symptom of sneezing was found to be the most easily influenced, with a reduction already within a week. A clear effect on nasal catarrh was noted during the second week of treatment, on itching during the third, and on nasal blocking during the fourth week. No serious side effects were registered, judged from analysis of cortisol/plasma, bacteriological, and partial mycological (*Candida albicans*) flora in the nasopharynx.

No previous study has been made before on this category of patients, i.e. patients with vasomotor rhinitis without polypoidosis. The material is therefore more uniform than material presented in other studies under the term of perennial rhinitis, where patients with both allergic and vasomotor rhinitis have been included. However, a comparison of our results with those from investigations with mixed material and investigations with allergic rhinitis might be of interest.

In the study of Gibson et al. (6) with 200 μ g beclomethasone dipropionate/day, 16 patients with allergic rhinitis and nine with vasomotor rhinitis took part. The corresponding figures for Hansen & Mygind (9) and Morrison Smith et al. (14) with 400 μ g/day were 15/6 and 28/17, respectively. Good results were obtained in all three investigations, with a preference for beclomethasone dipropionate rather than placebo of between 64 and 76 per cent. It is worth noting that Gibson et al. in their investigation with 200 μ g/day, found an effect which was well comparable with that of other studies using double the dose.

In purely allergic cases, for instance patients with hay fever, equally good or even better results have been registered in earlier studies. Thus, in Mygind's study (15) with 400 μ g beclomethasone dipropionate, 86 per cent of the patients reported a preference for beclomethasone. In a later study, Brown & Storey (1) have found 71 per cent to have good, and 7 per cent moderate control also with 400 μ g of beclomethasone dipropionate/day. In a previous report, we (11) could state that 95 per cent of the subjects regarded the treatment effective against nasal symptoms with 300 μ g/day.

Our treatment results presented here are consequently on a level with those reported by the above-mentioned investigators for perennial rhinitis, but somewhat less favourable than those for hay fever. It is also of interest when comparing results to note that Morrison Smith et al. (14), in their study of 17 cases of vasomotor rhinitis in a material of 45 patients, only had an improvement of about 50 per cent with beclomethasone dipropionate, i.e. considerably lower than in our study. Maybe

our more favourable results can be ascribed to a different intensity of symptoms.

In our study, the nasal symptoms differed in their resistance to therapy. Most easily influenced was sneezing, followed in descending order by nasal catarrh, itching, and nasal blocking. This is not quite in conformity with the results from the investigation by Gibson et al. (6), according to whom sneezing and itching were resistant to treatment, whereas nasal catarrh and blocking improved. The results are more in accordance with those of Hansen & Mygind (9) who recorded an effect as regards sneezing and nasal catarrh already after a few days in several patients. Since the explanation of this observation hardly seems to be connected with the duration of treatment, it may perhaps be reasonable to assign the discrepancy either to the degree of trouble or to the smaller dose used in the study of Gibson et al. (6).

In our earlier study of hay fever (11) we wished to use a smaller dose of beclomethasone dipropionate than previously in order to further reduce the risk of systemic hormonal side effects. This has also been the aim in the present study, which includes the determination of cortisol/plasma in 19 patients. As seen in Table 2, we have found a definite, but insignificant influence on the cortisol/plasma values after 4 weeks of treatment with beclomethasone dipropionate. This is perhaps of interest in cases with long-term therapy, and in this connection it is worth noting the results of Gibson et al. (6) who found no decrease of values with a dose of 200 μ g beclomethasone dipropionate.

Finally, it is evident from recent studies concerning bronchial asthma (3, 12, 13) that the risk of infection by *Candida albicans* is dependent on the dose and duration of treatment with beclomethasone dipropionate. From the results of this study it seems that 300 μ g of beclomethasone dipropionate a day for 4 weeks is too small an amount in too short a time to influence the flora of nasopharynx with regard to *Candida albicans* and bacteria.

SUMMARY

The effect of beclomethasone dipropionate (Becotide®) intranasally in vasomotor rhinitis has been studied on 39 adult volunteers in a double-blind cross-over study during 9 weeks in February–April 1975. The dose of beclomethasone dipropionate was 300 µg/day. Twenty-five patients preferred the beclomethasone dipropionate period, 5 patients the placebo period, and 9 patients had no preference. About three-quarters (74 per cent) of the patients considered themselves free of symptoms or greatly improved after the treatment with beclomethasone dipropionate. Statistical calculation of the daily nasal symptoms score confirms the improvement. The speediest effect was registered for sneezing, followed by nasal catarrh, nasal itching, and blocking. No changes in the levels of cortisol occurred during the treatment. The bacteriological and mycological findings (analysed with regard to *Candida albicans*) were fairly constant.

ACKNOWLEDGEMENTS

We wish to thank Nils-Gunnar Pehrsson, Chalmers University of Technology, Göteborg, for statistical calculation; and Glaxo Läkemedel AB, Sweden, for providing the aerosols used in this trial.

This investigation was supported by grants from Alfred Österlund's Stiftelse, Malmö, Sweden.

REFERENCES

1. Brown, H. M. & Storey, G. (1974): Beclomethasone dipropionate aerosol in the treatment of seasonal asthma and hay fever. *Clin. Allergy* 4, 331–341.
2. Capel, L. H. (1973): Rhinitis and allergy. In: Ransome, J., Holden, H. & Bull, T. R. (eds.): *Recent advances in otolaryngology*, pp. 235–251. Churchill Livingstone, Edinburgh and London.
3. Cayton, R. M., Soutar, C. A., Stanford, C. F., Turner, G. C. & Nunn, A. J. (1974): Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol in the treatment of chronic bronchial asthma. *Lancet* ii, 303–307.
4. De Moor, P., Steeno, O., Raskin, M. & Hendriks, A. (1960): Fluorimetric determination of free plasma 11-hydroxycorticosteroids in man. *Acta Endocrinol.* 33, 297–307.

5. De Moor, P., Osinki, P., Deckx, R. & Steeno, O. (1962): The specificity of fluormetric corticoid determinations. *Clin. Chim. Acta* 7, 475-480.
6. Gibson, G. J., Maberly, D. J., Lal, S., Ali, M. M. & Butler, A. G. (1974): Double-blind cross-over trial comparing intranasal beclomethasone dipropionate and placebo in perennial rhinitis. *Brit. med. J.* 4, 503-504.
7. Hansel, F. K. (1934): Observations on the cytology of the secretions in allergy of the nose and paranasal sinuses. *J. Allergy* 5, 357-366.
8. Hansel, F. K. (1953): *Clinical allergy*. The C. V. Mosby Company, St. Louis.
9. Hansen, I. & Mygind, N. (1974): Local effect of intranasal beclomethasone dipropionate aerosol in perennial rhinitis. *Acta allergol.* 29, 281-287.
10. Koch, H. (1947): Allergical investigations of chronic otitis. *Acta Oto-laryng. Suppl. LXII*, p. 51.
11. Löfkvist, T. & Svensson, G. (1975): An open assessment of Becotide® (Beclomethasone dipropionate) nasal spray in seasonal allergic rhinitis. *Acta allergol.* 30, 227-238.
12. McAllen, M. K., Kochanowski, S. J. & Shaw, K. M. (1974): Steroid aerosols in asthma: An assessment of Betamethasone valerate and a 12-month study of patients on maintenance treatment. *Brit. med. J.* 1, 171-175.
13. Milne, L. J. R. & Crompton, G. K. (1974): Beclomethasone dipropionate and oropharyngeal candidiasis. *Brit. med. J.* 3, 797-798.
14. Morrison Smith, J., Clegg, R. T., Cook, N. & Butler, A. G. (1975): Intranasal beclomethasone dipropionate in allergic rhinitis. *Brit. med. J.* 1, 255.
15. Mygind, N. (1973): Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. *Brit. med. J.* 4, 464-466.
16. Mygind, N., Brahe Pedersen, C., Prytz, S. & Sørensen, H. (1975): Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. *Clin. Allergy* 5, 159-164.
17. Sheldon & Lovell-Mathews (1967): *A manual of clinical allergy*, pp. 83-86. W. B. Saunders Company, Philadelphia and London.

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EFFECTS OF TOPICAL USE OF β -ADRENOCEPTOR STIMULANTS ON NASAL MUCOSA. RHINOMANOMETRIC EVALUATIONS IN EXPERIMENTS WITH TERBUTALINE AND KWD 2131

I. Normal Persons and Hay Fever Patients in Asymptomatic Period

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(Received August 6, 1979)

Abstract. The effects of nasal airway resistance of the β -adrenoceptor stimulants terbutaline (Bricanyl®) and KWD 2131 intranasally have been studied by means of posterior rhinomanometry in 16 healthy volunteers and 3 asymptomatic patients with allergic rhinitis. The study was performed as a randomized, placebo-controlled, double-blind crossover trial. No obvious changes in nasal resistance were revealed. This makes the nasal mucosa a suitable organ for testing the capacity of β -adrenoceptor stimulants to reduce the release of mediators from mast cells after allergen challenges.

The autonomous nervous system plays an important part in the regulation of tone in the nasal vascular bed. This has been shown in studies performed after sympathetic nerve stimulation and cervical sympathectomy and is also reflected by the successful clinical use of α -adrenoceptor stimulating drugs (Malcomson, 1959; Malm, 1973; Änggård & Densert, 1974).

It is well established that α -adrenoceptors predominate in the nasal vascular bed of man as well as of several animal species but opinions about the existence of β -adrenoceptors differ (Hall & Jackson, 1968; Malm, 1974; Hiley et al., 1978). A sparse distribution of β -adrenoceptors in the vessels of the human nasal mucosa cannot be excluded (McLean et al., 1976).

An anti-allergic effect is also ascribed to β -adrenoceptor stimulating drugs, i.e. they reduce mediator release from mast cells after

allergic provocation (Assem & Schild, 1969; Ishizaka et al., 1971; Kaliner & Austen, 1975). In patients with allergic rhinitis such an effect on the mast cells might imply reduced nasal congestion after allergic challenges and in periods of allergic symptoms.

The aim of this investigation was to evaluate any effect of β -adrenoceptor stimulants applied locally to the nasal mucosa, since the results of earlier studies on animals as well as humans are contradictory (Hall & Jackson, 1968; Malm, 1974; McLean et al., 1976; Hiley et al., 1978). Two trial groups—normal subjects and patients with seasonal allergic rhinitis—were studied, as a potential difference between them in sensitivity of possible β -adrenoceptors may exist, i.e. a quality of the nasal vessels similar to that of the bronchial muscles according to the hypothesis of Szentivanyi (1968). The obtained results could also be used as a background for an evaluation of the effect on mast cells of the tested substances in patients with allergic rhinitis in a consecutive study (Svensson, 1980).

MATERIAL AND METHODS

The study involved a total of 29 subjects (16 normal persons and 13 patients with allergic rhinitis). The normal volunteers (7 males and 9

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females), aged 24–38 years (average 31 years), had never had symptoms simulating allergic rhinitis, dermatitis, urticaria or bronchial asthma and had no heredity for these diseases. Analysis of IgE/serum with PRIST was within normal limits. The patients with seasonal allergic rhinitis (7 males and 6 females), aged 17–29 years (average 25 years), were asymptomatic during the trial. All of them were sensitive to pollen as shown by positive skin test and positive provocation test, and had suffered from hay fever during the last two seasons at least.

The preparations under investigation were two β -adrenoceptor stimulating drugs, terbutaline sulphate (Bricanyl®), dihydroxyphenyl ethanol sulphate (KWD 2131) and placebo (isotonic saline solution). Terbutaline 0.5 and 5 mg and KWD 2131 1.25 and 5 mg were administered to each nasal cavity. The dosage of terbutaline sulphate was based on experiences from treatment of asthmatic patients (McPhillips, 1977), from a high dosage tolerance study (Bennis & Svedmyr, 1977) and from a study of patients with allergic rhinitis performed in our laboratory (Hegardt & Svensson, 1977). The doses of KWD 2131 were based on results from studies on the protective property of nebulized (Hegardt et al., 1978) and subcutaneously (Pegelow & Strandberg, 1978) administered KWD 2131 in patients with asthma challenged with allergen and histamine. The drugs were applied locally as nose drops from a pipette in two equal portions (2×0.08 ml) to each nasal cavity with a time interval of 2 minutes between the portions.

During the drug application the subject was sitting with his/her head tilted backwards and laterally for administration against the lower turbinate. Placebo was delivered in the same volume and manner as terbutaline and KWD 2131. After each application the subject was questioned regarding any taste of drug, for evaluation of nasal and/or pharyngeal deposition. Experiments with suspected pharyngeal deposition of the drugs were put off to some

other day. When used, the drugs had the same temperature as the testing room, i.e. 22–23°C. In the meantime they were stored in a refrigerator (4–8°C).

The study, comprising six visits, was conducted in a double-blind crossover type and was conducted during a pollen-free period (January–March) in 1978. All subjects were asymptomatic as regards nasal symptoms and were free from drugs. The intervals between tests and each preparation were at least 2 days. The drugs were tested in a randomized order. Total nasal patency for both nasal cavities together (total nose) was determined during spontaneous breathing as posterior rhinomanometry.

Rhinomanometry

The nasal air flow was measured with a pneumotachograph attached to an ordinary nose mask (type Dräger) covering the nose and mouth. The pressure difference across the nose was estimated by recording pressure in the oropharynx through a catheter, held between teeth with lips closed and placed with its open tip in the oropharynx, and simultaneously recording pressure in the mask externally to the nares. Through electronic transducers the pressure difference was displayed on the Y-axis of a memory-oscilloscope screen and the flow on the X-axis. From standardized points of the pressure-flow curve, *ad modum* Broms et al. (1979), a mathematical description was obtained for each curve. From this description an angle v_2 between the curve and the flow-axis was calculated. Increasing values of v_2 denote higher nasal airway resistance. Differences between curves expressed as differences of v_2 were analysed statistically with Student's paired *t*-test. The proper value of nasal resistance out of v_2 for a total nose, $R = 5 \tan v_2$.

Prior to and after each test procedure the rhinomanometric equipment was calibrated in two steps. Firstly the deflections of pressure changes were adjusted with a stooping manometer and secondly the deflections of cor-

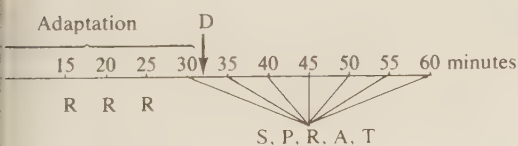
ated flow-pressure changes by means of a w over a known resistance.

The subjects were in a sitting position throughout the testing procedure. The first rhinomanometric determination was done after 15 minutes' adaptation to the testing room and repeated every 5 min. The preparations were administered after 30 minutes' stay in the testing room.

The condition of the nose was also recorded endoscopically as to the presence of oedema and secretion on a 0–3 scale (0=no symptoms, 1=mild, 2=moderate, 3=severe) before and every 5 min after application of the preparations. This examination was performed after the rhinomanometric evaluation. Also the patients' subjective opinion of nasal symptoms was recorded on a 0–3 scale. The pulse frequency was regularly determined before drug application and also before rhinomanometry. Hand tremor before and after drug administration was also recorded on a 0–3 scale. Because of acclimatization of the subject to the experimental situation, no statistical analyses were done until after 30 minutes' stay in the testing room.

The test procedure is given schematically as follows:

visits 1–6*



- = drug application
- = subjective evaluation
- = pulse-frequency determination
- = posterior rhinomanometry
- = anterior rhinoscopy
- = hand tremor examination

At visit 6 no drug was applied and the subjective evaluation, pulse-frequency determination, rhinoscopic and hand tremor examination were excluded.

For the allergic patients the effect of the lower doses of terbutaline, KWD 2131 and placebo was only followed after 15 min, as 0.5 mg terbutaline was without any obvious effect in a previous pilot study (Hegardt & Svensson, 1977).

The study was approved by the Ethical Committee of the University of Lund and informed consent was obtained from all patients.

RESULTS

Fig. 1 shows the mean basal nasal airway resistance (expressed as the angle ν_2) in the healthy volunteers and asymptomatic patients with allergic rhinitis in a sitting position. The values were somewhat higher for the allergic patients than for the normal volunteers, but these differences are not statistically significant. The variations of nasal airway resistance during 60 minutes' observation are small and without obvious differences between the groups.

Application of placebo to the nasal mucosa induced minor increases in the mean nasal airway resistance in both groups, but these increases were not statistically significant (Figs. 2 and 3). Terbutaline, 0.5 mg, and KWD 2131, 1.25 mg, evoked changes in the nasal airway resistance of about the same degree as placebo in both groups. Terbutaline, 5 mg, and KWD 2131, 5 mg (Figs. 2 and 3), induced a more marked increase in nasal airway resistance in both the healthy and allergic persons. These elevations were still small but statistically significant when they were analysed for each drug. However, in comparison with placebo there was neither any evident effect of terbutaline nor of KWD 2131 (Table I). The participants experienced no nasal changes during the experiments and the rhinoscopic examination revealed no alterations.

In the high dose, terbutaline induced tachycardia and tremor in all subjects. The pulse-frequency increased as early as 5 min after application of the drug, and remained increased during the whole experiment. The average increase was about 15–30 beats per minute. Tremor was noticed 5 min after application of the drug, but was pronounced after 10 min, and for the rest of the experiment. No other side effects were discovered.

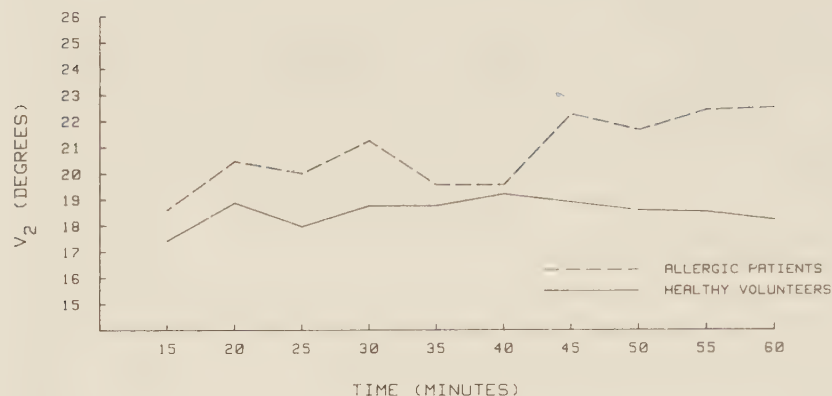


Fig. 1. Nasal airway resistance versus time. Mean values of 16 healthy volunteers and 13 patients with allergic rhinitis, respectively.

DISCUSSION

The basic aim of this investigation was to evaluate any effect of β -adrenoceptor stimulants locally applied to the nasal mucosa, as earlier studies on animals as well as humans are contradictory. In experiments on dogs Hall & Jackson (1968) could not demonstrate β -adrenoceptors in the nasal blood vessels. In cats, Änggård & Edwall (1974) found no β -adrenoceptors, but Malm (1974) has demonstrated such receptors in the resistance vessels and Hiley et al. (1978) in the capacitance vessels. The techniques (endotracheal tube, intra-arterial injections, cervical sympathetic trunk dissection and transection, surgical exploration of the pterygomaxillary fossa) used in these experiments could not be used in humans.

In three studies on humans (Grobler, 1966; Cohen, 1970; McLean et al., 1976) isoprenaline—a powerful stimulant of β_1 - as well as β_2 -adrenoceptors—has been used with different results. Grobler (1966) reported that the drug caused increased nasal airway resistance, but Cohen (1970) found no effect and McLean et al. (1976) registered a somewhat variable response with, in most instances, a greater decrease than after saline application. Methodological variations (different subject groups, various forms for administration of drugs, different types of equipment for measurement of nasal airway resistance and varying time points for this registration) make a comparison of the results of the three studies very difficult.

The study by McLean et al. (1976) can in several respects be compared with the present

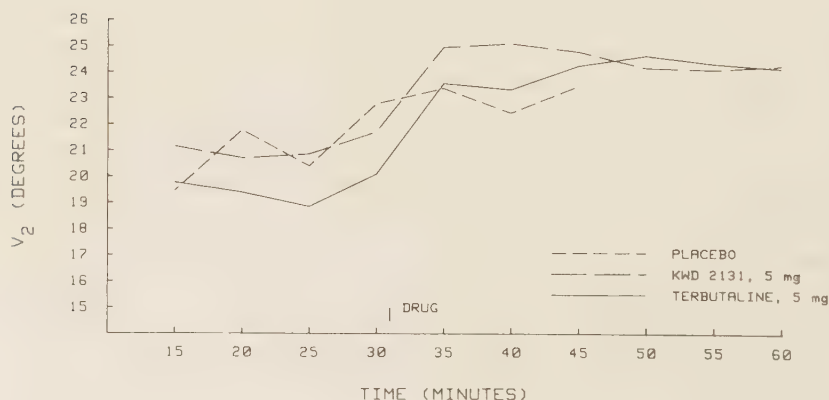


Fig. 2. Nasal airway resistance versus time. Mean values of 13 patients with allergic rhinitis.

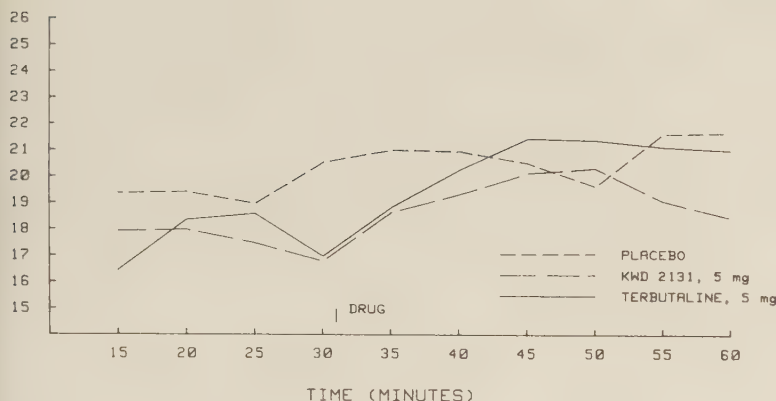


Fig. 3. Nasal airway resistance versus time. Mean values of 16 healthy volunteers.

investigation. Both deal with normal subjects and asymptomatic patients with hay fever, and make use of posterior rhinomanometry. The studies differ, however, with regard to the manner of drug application, to points of time for measurements and to the methods for calculation of nasal airway resistance. These differences might contribute to the difference in results. Moreover, McLean et al. (1976) used isoprenaline, while the present study was performed using terbutaline and KWD 2131, two substances with a more selective β_2 -adrenoceptor effect. Therefore, the differing characters of the drugs could also explain the non-corresponding results.

The method with topical application of sub-

stances presupposes local absorption of drugs. The nasal vascular bed seems to have a high capacity for absorption. Judging from the side effects—tachycardia and tremor—in the present experiments with terbutaline, 5 mg to each nasal cavity, this is in fact the case. Thus, β -adrenoceptors, if present in the human nasal vessels, should have been stimulated.

When β -adrenoceptors are stimulated, blood vessels commonly dilate. If the capacitance vessels in the human nasal mucosa contain β -adrenoceptors, their stimulation would evoke vasodilatation leading to increased nasal airway resistance, while a dilatation of the resistance vessels increases the blood flow with comparatively smaller changes in nasal

Table I. Comparison of the increase in nasal airway resistance, measured as v_2 relative to the 0 min value

Minute . . . Drugs compared	35 Increase in v_2	40	45	50	55	60
<i>Healthy persons:</i>						
Terbutaline 5 mg – placebo	1.4 n.s.	2.9 n.s.	4.5**	5.3**	3.1 n.s.	2.9 n.s.
Terbutaline 5 mg – no appl.	1.9 n.s.	2.9 n.s.	4.4*	4.6*	4.4*	4.6*
KWD 2131 5 mg – placebo	1.4 n.s.	2.2 n.s.	3.4*	4.5**	1.2 n.s.	0.5 n.s.
KWD 2131 5 mg – no appl.	1.9 n.s.	2.1 n.s.	3.3 n.s.	3.8*	2.6*	2.3 n.s.
KWD 2131 1.25 mg – no appl.	2.4 n.s.	0.7 n.s.	1.3 n.s.	2.3 n.s.	3.8**	3.1 n.s.
<i>Allergic patients</i>						
Terbutaline 5 mg – placebo	1.3 n.s.	5.0*	3.9 n.s.	–	–	–
KWD 2131 5 mg – placebo	1.9 n.s.	2.4*	2.3 n.s.	–	–	–

n.s.=not significant; *= $p<0.05$; **= $p<0.01$; –=Analysis not possible due to no registration of the effect of placebo after minute 45.

congestion. In the present study, subjective experiences, and rhinoscopic and rhinomanometric results after nasal application of the β -adrenoceptor stimulating drugs, used both in normal persons and in hay fever patients, showed only minor variations compared with the administration of placebo. These results indicate none or only few β -adrenoceptors of functional significance in the nasal mucosa, at least in the capacitance vessels. In consequence of this, a defect β -receptor function like that of asthmatic patients, according to the hypothesis of Szentivanyi (1968), could neither be established nor rejected in hay fever patients.

In hay fever patients, nasal provocations with appropriate allergens induce swelling of the nasal mucosa and higher nasal airway resistance due to the release of mediators from the mast cells. β -adrenoceptor stimulants are shown to inhibit the antigen-induced release of histamine in many tissues. For the nasal mucosa, treatment with β -adrenoceptor stimulants before nasal challenges would mean reduced swelling of the mucosa and, in consequence of this, decreased nasal airway resistance. Thus, the absence of demonstrable vascular effects in the nasal mucosa after application of β -adrenoceptor stimulants, as shown in this investigation, makes the nasal mucosa a suitable organ for testing the effect of β -adrenoceptor stimulating agents on mast cells.

ZUSAMMENFASSUNG

Die Wirkung der intranasalen β -adrenoceptorstimulierenden Substanzen Terbutaline (Bricanyl®) und KWD 2131 auf den Atemwiderstand der Nase wurde mit Hilfe der posterioren Rhinomanometrie an 16 gesunden freiwilligen Versuchspersonen und 13 asymptomatischen Patienten mit allergischer Rhinitis untersucht. Der Test wurde als ein doppelter Blindversuch unter Placebokontrolle durchgeführt. Es wurden keine Veränderungen im Atemwiderstand der Nase festgestellt. Dies zeigt, daß die nasale Schleimhaut ein brauchbares Organ für die Testung der Fähigkeit von β -adrenoceptorstimulierenden Substanzen ist, um die Freilassung der Mediatoren von Mastzellen nach allergischen Provokationstesten zu reduzieren.

REFERENCES

- Änggård, A. & Densert, O. 1974. Adrenergic innervation of the nasal mucosa in cat. A histological and physiological study. *Acta Otolaryngol* (Stockh) 78, 232-240.
- Änggård, A. & Edwall, L. 1974. The effects of sympathetic nerve stimulation on the tracer disappearance rate and local blood content in the nasal mucosa of the cat. *Acta Otolaryngol* (Stockh) 77, 131-139.
- Assem, E. S. K. & Schild, H. O. 1969. Inhibition of sympathomimetic amines of histamine release induced by antigen in passively sensitized human lung. *Nature* 224, 1028-1029.
- Bennis, J. & Svedmyr, N. 1977. A controlled comparison of salbutamol and terbutaline inhaled by IPPV in asthmatic patients: A dose-response study. *Scand J Respir Dis*, Suppl. 101, 113-117.
- Broms, P., Jonson, B. & Lamm, C. J. 1979. A unified way to evaluate the curve in rhinomanometry. *Acta Otolaryngol* (Stockh) Suppl. 360, 22-23.
- Cohen, B. M. 1970. The nasal respiratory handicap in expiratory airflow disease: The response to bronchodilator aerosols. *Respiration* 27, 406-416.
- Grobler, N. J. 1966. *Reactivity of the Nasal Respiratory Mucosa (A Clinical and Epidemiological Study)*. Thesis. Drukkerij van Denderen, Groningen.
- Hall, L. J. & Jackson, R. T. 1968. Effects of alpha and beta adrenergic agonists on nasal blood flow. *Ann Otol Rhinol Laryngol* 77, 1120-1130.
- Hegardt, B., Lindholm, B., Löwhagen, O. & Svedmyr, N. 1978. Evaluation of the anti-allergic property of nebulized KWD 2131. 13th Scandinavian Congress of Allergology 1978. *Allergy* 33, 332-333.
- Hegardt, B. & Svensson, G. 1977. Unpublished data.
- Hiley, C. R., Wilson, H. & Yates, M. S. 1978. Identification of β -adrenoceptors and histamine receptors in the cat nasal vasculature. *Acta Otolaryngol* (Stockh) 78, 444-448.
- Ishizaka, T., Ishizaka, K., Orange, R. P. & Austen, K. F. 1971. Pharmacologic inhibition of the antigen-induced release of histamine and slow reacting substance of anaphylaxis (SRS-A) from monkey lung tissues mediated by human IgE. *J Immunol* 106, 1267-1273.
- Kaliner, M. & Austen, K. F. 1975. Immunologic release of chemical mediators from human tissues. *Annu Rev Pharmacol* 15, 177-189.
- Malcomson, K. G. 1959. The vasomotor activities of the nasal mucous membrane. *J Laryngol Otol* 73, 73-98.
- Malm, L. 1973. Stimulation of sympathetic nerve fibres to the nose in cats. *Acta Otolaryngol* (Stockh) 75, 519-526.
- Malm, L. 1974. β -adrenergic receptors in the vessels of the cat nasal mucosa. *Acta Otolaryngol* (Stockh) 77, 242-246.
- McLean, J. A., Mathews, K. P., Ciarkowski, A. A., Brayton, P. R. & Solomon, W. R. 1976. The effect of topical saline and isoproterenol on nasal airway resistance. *J Allergy Clin Immunol* 58, 563-574.
- McPhillips, J. J. 1977. Terbutaline. In *Pharmacological and Biochemical Properties of Drug Substances* (ed. M. E. Goldberg), pp. 311-328. American Pharmaceutical Association, Washington, D.C.

elow, K.-O. & Strandberg, K. 1978. Evaluation of the antiallergic property of a β -adrenoceptor stimulator, KWD 2131, given subcutaneously. Methodological aspects. 13th Scandinavian Congress of Allergology 1978. *Allergy* 33, 333.

nnsson, G. 1980. Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. II. Nasal provocation tests with hay fever patients in asymptomatic period. *Acta Otolaryngol* (Stockh) 90, 130.

Szentivanyi, A. 1968. The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J Allergy* 42, 203-232.

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EFFECTS OF TOPICAL USE OF β -ADRENOCEPTOR STIMULANTS
ON NASAL MUCOSA. RHINOMANOMETRIC EVALUATIONS
IN EXPERIMENTS WITH TERBUTALINE AND KWD 2131

II. *Nasal Provocation Tests with Hay Fever Patients in Asymptomatic Period*

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(Received August 6, 1979)

Abstract. The effects of the β -adrenoceptor stimulating drugs, terbutaline (Bricanyl®) and KWD 2131, on the increase in nasal airway resistance induced by pollen extracts, have been studied in a placebo-controlled double-blind crossover trial of 13 asymptomatic (out of season) patients with hay fever. For objective evaluation of the nasal airway resistance posterior rhinomanometry has been used. The rhinomanometric measurements indicated an antianaphylactic effect of terbutaline and KWD 2131, but rhinoscopy and the patients' own opinion could not establish such an effect. The design of the trial made it possible to establish whether or not an increased or a decreased nasal obstruction due to repeated challenges occurred. Despite 6 preceding nasal provocations in each participant, neither increased ('priming effect') nor decreased (hyposensibilization) reaction was detected in the following challenge.

Sörenby, 1975). Experimental data have demonstrated that β -adrenoceptor-stimulating agents increase the tissue level of cyclic AMP. Moreover, an inverse dose-response relationship is stated between the tissue concentration of cyclic AMP and the capacity for immunologic induction of the secretion of chemical mediators. However, the role of cyclic AMP in histamine release has been questioned recently (Diamant et al., 1978).

Clinical studies also support the usefulness of β -adrenoceptor stimulation for blocking the immediate hypersensitivity reactions. Thus, Shereff et al. (1973) and Lamkin et al. (1976) could diminish skin test reaction in atopic subjects after iontophoretic application of isoprenaline. The same effect was also documented for terbutaline alone (Grönneberg et al., 1978) and for both terbutaline and KWD 2131 (Hegardt & Arner, 1978). Systematically administered adrenalin and isoprenaline to allergic patients reduced the wheal and flare reaction (Kram et al., 1975). This was also shown in rhesus monkeys after administration of salbutamol (Perper et al., 1972). Furthermore, chronic urticaria has been successfully treated with terbutaline (Kennes et al., 1977).

Two published studies concerning the effect of β -adrenoceptor stimulants on nasal allergic symptoms have reported contradictory results. In a study by Jorde et al. (1975) nasal application of fenoterol and salbutamol had a prophylactic as well as curative effect in nasal

Extrinsic asthma, hay fever, and the wheal and flare reaction in skin may all be considered as local manifestations of the immediate (Type I) anaphylactic reaction. As early as over four decades ago, Tuft & Brodsky (1936) showed that adrenalin suppressed the reagin-dependent wheal and flare reaction in human skin, and Schild (1936) demonstrated that adrenalin reduced the immunologic release of histamine from guinea pig lung tissue. Subsequently, a variety of sympathomimetic amines were shown to be capable of inhibiting the immunologic release of mediators from rat mast cells, guinea pig lung as well as human lung, leukocytes, and nasal polyps (Assem & Schild, 1969; Orange et al., 1971; Kaliner et al., 1973; Kaliner & Austen, 1974; Sörenby, 1974a, b; Kaliner & Austen, 1975; Lichtenstein, 1975;

provocation tests. The results of McLean et al. (1976) did not convincingly show such an effect of isoprenaline. Placebo was not used in the two trials, and Jorde et al. (1975) did not describe the technique for allergen provocation. Moreover, the results of Jorde et al. (1975) contrasted with an unpublished placebo-controlled double-blind crossover study performed in our laboratory on 20 patients with perennial allergic rhinitis due to house dust, who were treated orally with terbutaline for 2 weeks (Svensson, 1974). In this study, placebo was as good as terbutaline (5 mg $\times$ 3) in diminishing the patients' nasal troubles. However, in another unpublished pilot study of the prophylactic effect of nasal application of terbutaline (0.5 mg to each nasal cavity) to 9 asymptomatic patients with hay fever, rhinomanometric registrations of nasal patency before and after nasal provocations showed terbutaline to be superior to placebo in diminishing nasal obstruction due to challenges (Hegardt & Svensson, 1977).

One purpose of the present study was to gain further experience of the antianaphylactic effect of terbutaline. A second purpose was to evaluate the effect of a new β -adrenoceptor agonist, KWD 2131, which in animal experiments had shown the same antianaphylactic action, but lower cardiovascular and bronchodilating effects than terbutaline (Sörenby, 1977). Based on these data, KWD 2131 seemed to offer some advantages as a drug in nasal allergy, and a comparison between the two drugs in human experiments should be of interest. In such a study, repeated nasal allergen provocations in the same patients had to be done with hyposensitization or 'priming effect', i.e. decreased or increased reactions, as possible consequences. Thus, a third purpose of the study was to reveal a changed reactivity of the nasal mucosa due to the experiments.

MATERIAL AND METHODS

The trial was conducted over a pollen-free period of 3 months, January–March, 1978.

A total of 13 patients (7 males and 6 females, aged 17–29 years, average 25 years) with seasonal allergic rhinitis, were included in the trial. All of them were asymptomatic (out of season) but sensitive to pollen as shown by positive skin test and positive provocation test, and they had suffered from hay fever during the last two seasons at least. Any patient exhibiting nasal polyps or asthmatic symptoms was excluded.

The preparations under investigation were two β -adrenoceptor stimulating drugs, terbutaline sulphate (Bricanyl® provided by AB Draco, subsidiary to AB Astra, Sweden), dihydroxyphenyl ethanol sulphate (KWD 2131, AB Draco) and placebo (isotonic saline solution). The dosage of terbutaline was 0.5 and 5 mg and for KWD 2131 1.25 and 5 mg to each nasal cavity. The drugs were applied locally as nose drops from a pipette in two equal portions (2 $\times$ 0.08 ml) to each nasal cavity with a time interval of 2 minutes between the portions. During the drug application the subject was sitting with his/her head tilted backwards and laterally for administration against the lower turbinate. Placebo was delivered in the same volume and manner as terbutaline and KWD 2131. After each application, the subject was asked for any taste of drug for evaluation of nasal and/or pharyngeal deposition. Experiments with suspected pharyngeal deposition of the drugs were put off to another day. When used, the drugs had the same temperature as the testing room, i.e. 22–23°C. In the meantime they were stored in a refrigerator (4–8°C).

The nasal provocations were performed with the disc method (Okuda, 1977) which involves small paper discs (squares with sides of 8 mm) soaked with 0.05 ml allergen solution being attached to the anterior part of one lower turbinate. At each visit, the less swollen turbinate was selected for provocation. First, two things were determined: the suitable concentration of the allergen solution, and the duration of provocation for each volunteer to induce a positive provocation reaction in the

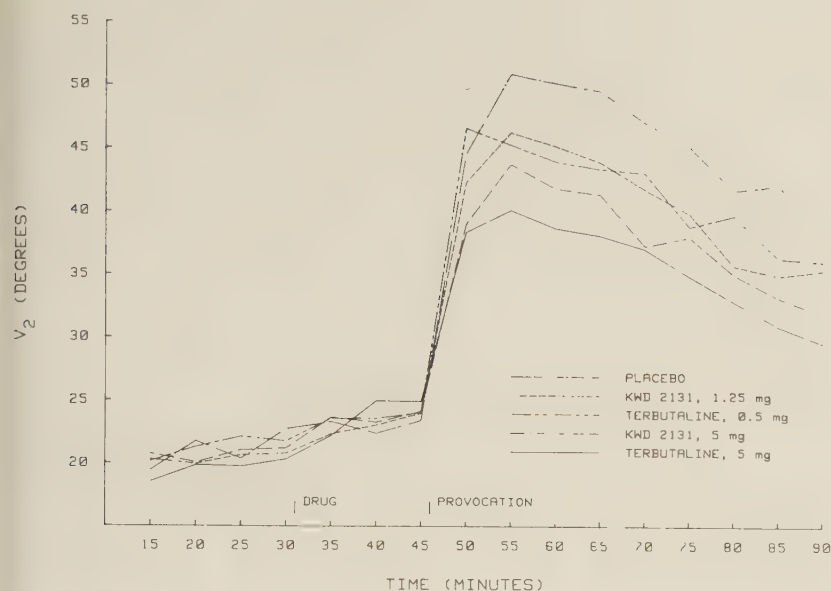


Fig. 1. Nasal airway resistance versus time. Mean values of 13 patients with allergic rhinitis.

nasal mucosa. For each person, the same allergen concentration (1 : 100 in Coca's solution (Philips, 1967) for all subjects and 1 : 10 for 2 subjects not reacting on 1 : 100) and duration of provocation (3 or 5 min) were used in all experiments.

The study included 7 visits with nasal challenges—5 preceded by treatment with terbutaline, KWD 2131 and placebo in a double-blind crossover manner for evaluation of antianaphylactic effects of the substances, and 2 (the first and last) provocations without any pretreatment with drugs for determinations of nasal hyposensitization or 'priming effect'. On these two occasions, instead of treatment with drugs, a disc soaked in Coca's solution was applied to the anterior part of the lower turbinate for 4 min. This was done 15 min before the succeeding allergen provocation in order to evaluate the mechanical effects of the disc.

The interval between each provocation was 1 or 2 weeks. The drugs were tested in a randomized order. Each subject was interviewed and medically examined (rhinoscopy for evaluation of nasal obstruction and secretion, pulse-frequency determination and hand tremor examination for evaluation of side ef-

fects) before entry into the trial as well as before, during and after each testing. All subjects were asymptomatic as to nasal symptoms before each provocation and free from drugs.

The stock solution of allergen (1 : 10) was stored in a refrigerator throughout the experiment, and new dilutions were prepared each week. These were also stored in a refrigerator until 45 min before using. The effects of the provocations were observed for 45 min. Eleven patients were challenged with timothy (*Phleum pratense*) solution, one with broad-leaf tree (*Alnus glutinosa*, *Betula verrucosa* and *Corylus avellana*) solution, and one with mugwort (*Artemisa vulgaris*) solution.

The nasal patency was evaluated with posterior rhinomanometry. The first rhinomanometric determination was done after 15 minutes' adaptation to the testing room and repeated every 5 min. The preparations were administered after 30 min and the nasal challenges carried out after 45 minutes' stay in the testing room. The condition of the nose was also recorded rhinoscopically as to the presence of oedema and secretion on a 0–3 scale (0=no symptoms, 1=mild, 2=moderate, 3=severe) before and every 5 min after application of the preparations and the nasal

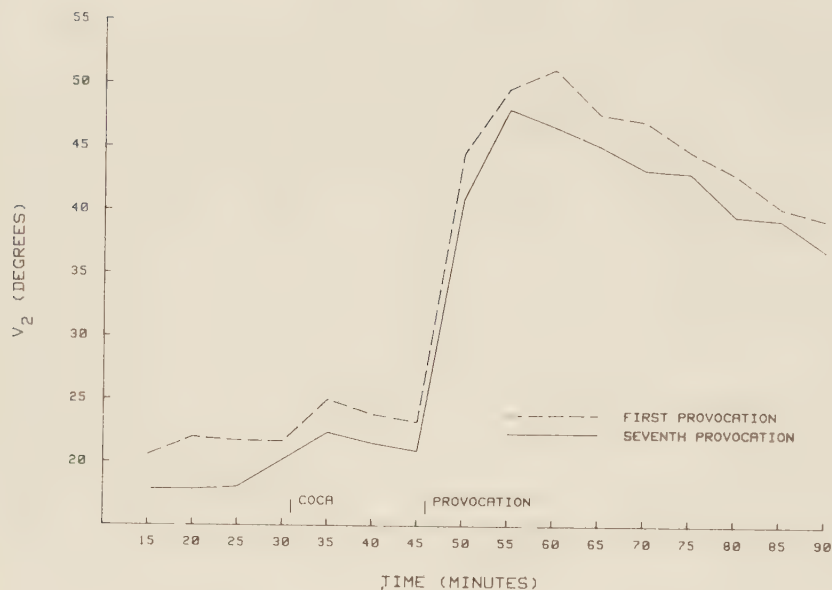


Fig. 2. Nasal airway resistance versus time. Mean values of 13 patients with allergic rhinitis.

challenges. This examination was performed after the rhinomanometric evaluation. Also, the patients' subjective opinion of nasal symptoms was recorded on a 0–3 scale. The pulse frequency was regularly determined before drug application and before rhinomanometry. Hand tremor before and after drug administration was also recorded on a 0–3 scale.

The test procedure is given schematically as follows:



- C = nasal challenge
- D = drug or Coca disc application
- S = subjective evaluation
- P = pulse-frequency determination
- R = posterior rhinomanometry
- A = anterior rhinoscopy
- T = hand tremor examination

Rhinomanometry

The nasal airway resistance for both nasal cavities together (total nose) was determined during spontaneous breathing as posterior rhinomanometry in a sitting position, using the technique of Broms et al. (1979) for evalua-

tion of the results. Thus, an angle v_2 , as a measure of nasal airway resistance, was calculated. Details have been given in a previous study (Svensson et al., 1979). Increasing values of v_2 denote increasing nasal airway resistance.

The differences in angle v_2 were analysed statistically with Student's paired *t*-test.

Because of acclimatization of the subject to the experimental situation, no statistical analyses were done until after 30 minutes' stay in the testing room.

The study was approved by the Ethical Committee of the University of Lund and informed consent was obtained from all patients.

RESULTS

Fig. 1 shows the changes in nasal airway resistance, expressed as the angle v_2 , under different conditions (adaptation, after treatment with terbutaline and KWD 2131, placebo, and after nasal provocation). It is obvious that pre-treatment with the actual drugs caused only minor changes in nasal resistance. This was also in agreement with the patients' subjective opinion and the rhinoscopic findings.

The changes in nasal airway resistance be-

fore and after application of a paper disc with Coca's solution to the lower turbinate are seen in Fig. 2. This treatment of the nose resulted immediately in an increased nasal airway resistance. These increases are small but statistically significant. However, the mean value was gradually reduced to almost the preapplication value 10 min after extraction of the disc. The rises in nasal airway resistance after application of the disc were also compared with those induced by administration of placebo into the nose. No statistically significant differences in the capacity of changing nasal airway resistance were revealed between the two methods. The participants experienced no nasal changes during the experiments, and the rhinoscopic examination revealed no changes.

The rhinomanometric determinations of nasal patency just before provocation, minute 45 (Fig. 1), did agree fairly well between the treatment groups.

The nasal provocations at minute 45 were followed by marked increases in nasal air flow resistance. Compared with the values before provocation, all these increases in nasal airway resistance were highly statistically significant. Also, the patients' subjective opinion and the rhinoscopic findings supported the rhinomanometric determinations.

The nasal provocation without pretreatment (Fig. 2) or after pretreatment with placebo (Fig. 1) caused the most pronounced increases in nasal airway resistance. Pretreatment with KWD 2131 1.25 mg, terbutaline 0.5 mg, KWD 2131 5 mg and terbutaline 5 mg to each nasal cavity were in the given sequence followed by gradually diminishing increases in nasal resistance. Thus, the best protection was given by terbutaline 5 mg and KWD 2131 5 mg. Compared with placebo pretreatment, these doses of the two substances caused diminished increases in nasal airway resistance after nasal provocation (Table I). This effect was statistically significant. A reduced increase was also found after terbutaline 0.5 mg, but this effect was less conspicuous.

The rhinoscopic findings and the patients' own opinions about the symptoms after nasal challenges revealed no evident differences between pretreatment with terbutaline, KWD 2131, or placebo.

Increased pulse frequency and hand tremor were found in all patients when 5 mg terbutaline was administered to each nasal cavity. One patient was also troubled by tremor of the hands after administration of the low dose (0.5 mg) of terbutaline and the high dose (5 mg) of KWD 2131. In another 2 patients tremor was suspected after application of the low dose of terbutaline.

A comparison of the results obtained at the first and last nasal provocation—both without pretreatment with any drug—gave an evaluation of the effect of repeated nasal challenges. It was obvious that six earlier provocations neither diminished nor increased the airway resistance in the following (the seventh) nasal provocation (Fig. 2). Moreover, six challenges did not change the nasal reactions after application of a disc without allergen, i.e. a non-allergic stimulus (Fig. 2).

DISCUSSION

Sympathomimetic amines inhibit antigen-induced release of histamine in many tissues (Assem & Schild, 1969; Kaliner et al., 1973; Sörenby, 1974a; Kaliner & Austen, 1975). The inhibiting effect of histamine release is blocked by propranolol, indicating involvement of β -adrenoceptors. The β -adrenoceptor stimulants, isoprenaline, orciprenaline, and terbutaline sulphate, show inhibition of anaphylactic histamine release in the guinea pig lung in the same concentrations as they exert tracheorelaxation (Sörenby, 1975). Therefore, allergen provoked bronchoconstriction does not seem to be a suitable model for the examination of the antiallergic effect of these drugs. The nasal mucosa, however, with no or only a few β -adrenoceptors in the vessels (Svensson et al., 1979), should be a better organ for an evaluation of this effect.

Table I. Comparison of the increase of nasal airway resistance, measured as v_2 , relative to 45 min value

Minute ... Drugs compared	50 Increase in v_2	55	60	65	70	75
Placebo - Terb 5 mg	7.7*	12.3**	13.0**	13.0**	11.6**	11.8**
Placebo - Terb 0.5 mg	-1.4 n.s.	6.3*	6.9**	6.8*	4.7 n.s.	7.0 n.s.
Placebo - KWD 2131 5 mg	6.3*	7.9*	9.1**	9.0**	10.5**	7.9*
Placebo - KWD 2131 1.25 mg	2.8 n.s.	5.3 n.s.	5.6 n.s.	6.2 n.s.	5.9*	5.9 n.s.
KWD 2131 5 mg - Terb 5 mg	1.4 n.s.	4.4 n.s.	3.9 n.s.	4.0 n.s.	1.0 n.s.	3.9 n.s.
Terb 0.5 mg - KWD 2131 1.25 mg	4.2 n.s.	-1.1 n.s.	-1.3 n.s.	-0.6 n.s.	1.2 n.s.	-1.1 n.s.

n.s. = not significant; * = $p < 0.05$; ** = $p < 0.01$.

In therapeutic oral doses, the conventional β -adrenoceptor stimulants often cause side effects such as tachycardia and tremor. In animals (Sörenby, 1977) KWD 2131 exhibited an antiallergic effect similar to that of terbutaline, but less pronounced cardiovascular and bronchodilating effects. A clinical study of healthy volunteers (Pegelow & Strandberg, 1978), including measurements of heart rate, blood pressure and tremor, showed terbutaline to be about 10 times as potent as KWD 2131 with respect to cardiovascular effects. The profile of action for KWD 2131, i.e. an appreciable antianaphylactic effect in concentrations causing negligible bronchodilating and cardiovascular effects, makes the substance an interesting tool for clinical evaluation of antianaphylactic effects.

As no previous study had been performed with terbutaline and KWD 2131 applied to the nose, various doses had to be evaluated with respect to antianaphylactic effect. The low dose of terbutaline (0.5 mg to each nasal cavity) was based on experiences from ordinary treatment of asthmatic patients (McPhillips, 1977) and from a pilot study on patients with allergic rhinitis (Hegardt & Svensson, 1977). The high dose (5 mg) was chosen considering the fact that no obvious side effects were observed after inhalation of 5 mg terbutaline (Bennis & Svedmyr, 1977). The low dose of KWD 2131 (1.25 mg to each nasal half) was previously shown to have doubtful or weak antiallergic properties (Hegardt et al., 1978; Pegelow & Strandberg, 1978).

Application of discs is one of the methods for nasal provocation tests. According to Okuda (1977) the disc method is suitable without disturbing nasal reactions. However, he based his opinion on rhinoscopy only. In the present study, using rhinomanometry, it was found that the nasal airway resistance increased but returned to about the same value as before the application of the disc within 10 min after the extraction of the disc. It did not differ from administration of placebo in changing the nasal resistance. Thus, our method for application of disc seems to be suitable for nasal provocation.

The nasal airway resistance after allergen challenges, evaluated with posterior rhinomanometry, decreased after pretreatment with terbutaline and KWD 2131 compared with placebo (Fig. 1). The differences between terbutaline 5 mg and placebo as well as between KWD 2131 5 mg and placebo were statistically significant (Table I), suggesting an antianaphylactic effect of the substances at these dosages. Such an effect, but less distinct, was also observed after terbutaline 0.5 mg (Table I). Comparisons between the rhinomanometric results obtained after terbutaline 5 mg and KWD 2131 5 mg showed no significant differences (Table I). This ought to signify a comparable antianaphylactic effect of the two substances at the given dosage. These results are in agreement with those obtained in experiments on animals (Sörenby, 1977), and also with the results on skin reactions (Hegardt & Arner, 1978).

	85	90
0.4*	12.8**	10.1*
1.7 n.s.	6.5 n.s.	2.7 n.s.
7.4*	9.7*	7.0*
1.6 n.s.	7.8 n.s.	3.3 n.s.
3.0 n.s.	3.1 n.s.	3.1 n.s.
3.9 n.s.	1.3 n.s.	0.6 n.s.

In contrast to the lower dose (0.5 mg) of terbutaline, that of KWD 2131 (1.25 mg) did not show any antianaphylactic effect compared with placebo (Table I). This agrees with the results from studies on asthmatic patients (Hegardt et al., 1978; Pegelow & Strandberg, 1978), but is, on the other hand, somewhat surprising with respect to the comparable anti-anaphylactic effect demonstrated in experiments on animals (Sörenby, 1977) and with the higher dose in this study. Different slopes of the dose-response curves for terbutaline and KWD 2131, or a displacement to the right for that of KWD 2131, could perhaps offer an explanation for this divergence.

The present results are in accordance with those drawn from a pilot study (Hegardt & Svensson, 1977) using topical terbutaline in hay fever patients. Jorde et al. (1975) in their study with fenoterol and salbutamol also found a prophylactic effect of these substances in allergic rhinitis: judging from their graphical illustration, the effect of fenoterol seemed to be more pronounced than that of terbutaline and of KWD 2131 in the present trial. In the study by McLean et al. (1976), local application of isoprenaline prior to ragweed challenges produced either a variable inhibition of the increases in nasal airway resistance or no protection at all. The disparity of the results could be due to methodological variations. Jorde et al. (1975) have not given details of the provocation procedure and McLean et al. (1976) have used a provocation technique with an expected increase in the nasal airway

resistance of about 200%. Of course, a weak antiallergic effect cannot neutralize a very strong provocation reaction. In the present study, with a demonstrable antiallergic effect of the two β_2 -adrenoceptor stimulants, the increases in angle v_2 after challenge were about 100%, corresponding to an increase in nasal airway resistance of 100–150% ($R=5 \tan v_2$).

The antianaphylactic effects of terbutaline and KWD 2131 in this study are based on rhinomanometry. The clinical relevance of these effects is fundamental and the rhinoscopic findings, the patients' own opinion, and any side effects must be evaluated. In this study the rhinoscopic findings and the patients' own opinions did not reveal any obvious differences between the substances. For a better evaluation of the antiallergic effect, a clinical trial with registration of the subjects' symptoms on diary cards during a pollen season might be of interest. However, the side effects of administering 5 mg terbutaline to each nasal cavity found in the present study preclude further investigations with terbutaline. With respect to this, KWD 2131 should be preferred.

The design of the present study made it possible to estimate the development of 'priming effect' or nasal hyposensibilization. 'Priming effect' is a phenomenon characterized by an increased reactivity of nasal or bronchial mucosa following repeated exposures to allergen. Moreover, when the 'priming effect' is established, environmental factors which normally do not produce reactions in the shock organ can then induce such reactions (Connell, 1969). Hyposensibilization is a phenomenon in the opposite direction, i.e. a decreased reactivity of the challenged mucosa following repeated exposures to allergen. Nasal hyposensibilization due to repeated nasal treatment with different antigenic preparations has been described by several authors (Gleich & Yunginger, 1975; Mehta & Morrison Smith, 1975; Deuschl & Johansson, 1977). In the present study the first and last visit for the volunteers included, without pre-

treatment with drugs, the application of a disc soaked with Coca's solution and thereafter provocation with allergen. Comparing the reactions after the application of a disc with Coca's solution no differences between the two visits were found, indicating an unchanged reactivity to environmental factors. Nor were there any differences in response to allergen. Thus, in the present trial neither 'priming effect' nor nasal hyposensibilization could be demonstrated.

ZUSAMMENFASSUNG

Die Wirkung der β -adrenoceptorstimulierenden Substanzen, Terbutaline (Bricanyl®) und KWD 2131, in bezug auf die Erhöhung des Atemwiderstandes der Nase durch Pollenextrakte war Gegenstand eines placebo-kontrollierten doppelten Blindversuches an 13 asymptomatischen Patienten mit Heufieber. Zur objektiven Bestimmung des Atemwiderstandes der Nase wurde die posteriore Rhinomanometrie angewandt. Die rhinomanometrischen Messungen zeigten einen antianaphylaktischen Effekt von Terbutaline und KWD 2131 an, aber sowohl Rhinoskopie als subjektive Empfindung der Patienten konnten einen solchen Effekt nicht bestätigen.

Die Anordnung der Untersuchung machte es möglich festzustellen, ob eine verstärkte oder geschwächte Schwellung der nasalen Schleimhaut aufgrund wiederholter Untersuchungen eintrat oder nicht. Trotz 6 vorangegangener Untersuchungen an jeder Versuchsperson wurde in der folgenden Untersuchung weder eine verstärkte („priming-Effekt“) noch geschwächte (Desensibilisierungs-)Reaktion festgestellt.

REFERENCES

- Assem, E. S. K. & Schild, H. O. 1969. Inhibition by sympathomimetic amines of histamine release induced by antigen in passively sensitized human lung. *Nature* 224, 1028–1029.
- Bennis, J. & Svedmyr, N. 1977. A controlled comparison of salbutamol and terbutaline inhaled by IPPV in asthmatic patients: A dose-response study. *Scand J Respir Dis*, Suppl. 101, 113–117.
- Broms, P., Jonson, B. & Lamm, C. J. 1979. A universal way to evaluate the curve in rhinomanometry. *Acta Otolaryngol* (Stockh), Suppl. 360, 22–23.
- Connell, J. T. 1969. Quantitative intranasal pollen challenges. III. The priming effect in allergic rhinitis. *J Allergy* 43, 33–44.
- Deuschl, H. & Johansson, S. G. O. 1977. Hyposensitization of patients with allergic rhinitis by intranasal administration of chemically modified grass pollen allergen. A pilot study. *Acta Allergol* 32, 248–262.
- Diamant, B., Kazimierzczak, W. & Patkar, S. A. 1978. Does cyclic AMP play any role in histamine release from rat mast cells. *Allergy* 33, 50–51.
- Gleich, G. J. & Yunginger, J. W. 1975. Ragweed hay fever: Treatment by local passive administration of IgG-antibody. *Clin Allergy* 5, 79–87.
- Grönneberg, R., Strandberg, K. & Hägermark, Ö. 1978. Selective inhibition of allergen induced cutaneous responses by terbutaline, a β -adrenergic receptor stimulating compound. 13th Scandinavian Congress of Allergology 1978. *Allergy* 33, 334.
- Hegardt, B. & Arner, B. 1978. Anti-allergiska effekter av en ny β -agonist, KWD 2131, och terbutalin (Bricanyl®) på allergen-inducerade intrakutana reaktioner. Föredrag vid sektionen för invärtesmedicinsk allergologi, Medicinska Riksstämman, Stockholm.
- Hegardt, B., Lindholm, B., Löwhagen, O. & Svedmyr, N. 1978. Evaluation of the anti-allergic property of nebulized KWD 2131. 13th Scandinavian Congress of Allergology 1978. *Allergy* 33, 332–333.
- Hegardt, B. & Svensson, G. 1977. Unpublished data.
- Jorde, W., Bohlmann, H.-G., Linsenmann, P. & Werdermann, K. 1975. Protektive Wirkung von beta-adrenergen Substanzen bei der allergischen Rhinitis. *Med Klin* 70, 1314–1316.
- Kaliner, M. & Austen, K. F. 1974. Cyclic AMP, ATP, and reversed anaphylactic histamine release from rat mast cells. *J Immunol* 112, 664–674.
- Kaliner, M. & Austen, K. F. 1975. Immunologic release of chemical mediators from human tissues. *Annu Rev Pharmacol* 15, 177–189.
- Kaliner, M., Wasserman, S. I. & Austen, K. F. 1973. Immunologic release of chemical mediators from human nasal polyps. *N Engl J Med* 289, 277–281.
- Kennes, B., De Maubeuge, J. & Delespessie, G. 1977. Treatment of chronic urticaria with a beta₂-adrenergic stimulant. *Clin Allergy* 7, 35–39.
- Kram, J. A., Bourne, H. R., Maibach, H. I. & Melmon, K. L. 1975. Cutaneous immediate hypersensitivity in man: Effects of systemically administered adrenergic drugs. *J Allergy Clin Immunol* 56, 387–392.
- Lamkin, Jr, N., Lieberman, P., Shereff, R., Rosenberg, E. W. & Robinson, H. 1976. Effect of beta adrenergic stimulation and blockade on cutaneous reactivity to histamine. *J Allergy Clin Immunol* 57, 449–453.
- Lichtenstein, L. M. 1975. Sequential analysis of the allergic response: Cyclic AMP, calcium and histamine. *Int Arch Allergy Appl Immunol* 49, 143–154.
- McLean, J. A., Mathews, K. P., Ciarkowski, A. A., Brayton, P. R. & Solomon, W. R. 1976. The effects of topical saline and isoproterenol on nasal airway resistance. *J Allergy Clin Immunol* 58, 563–574.
- McPhillips, J. J. 1977. Terbutaline. In *Pharmacological and Biochemical Properties of Drug Substances* (ed. M. E. Goldberg), pp. 311–328. American Pharmaceutical Association, Washington, D.C.
- Mehta, S. B. & Morrison Smith, J. 1975. Nasal hyposensitization and hay fever. *Clin Allergy* 5, 279–284.
- Okuda, M. 1977. Basic study of nasal provocative test. First report: Side, site of the nose, size of site and allergen amount. *Arch Oto-Rhino-Laryngol* 214, 241–246.

- Orange, R. P., Austen, W. G. & Austen, K. F. 1971. Immunological release of histamine and slow-reacting substance of anaphylaxis from human lung. I. Modulation by agents influencing cellular levels of cyclic 3',5'-adenosine monophosphate. *J Exp Med* 134, 136s–148s.
- Pegelow, K.-O. & Strandberg, K. 1978. Evaluation of the antiallergic property of a β -adrenoceptor stimulator, KWD 2131, given subcutaneously. Methodological aspects. 13th Scandinavian Congress of Allergology 1978. *Allergy* 33, 333.
- Perper, R. J., Sanda, M. & Lichtenstein, L. M. 1972. The relationship of *in vitro* and *in vivo* allergic histamine release: Inhibition in primates by cAMP active agents. *Int Arch Allergy Appl Immunol* 43, 837–844.
- Philips, G. L. 1967. Preparation of allergenic extracts for testing and treatment. In *A Manual of Clinical Allergy* (ed. J. M. Sheldon, R. G. Lovell & K. P. Mathews), 2nd edn., pp. 507–531. W. B. Saunders Company, Philadelphia and London.
- Schild, H. 1936. Histamine release and anaphylactic shock in isolated lungs of guinea-pigs. *Q J Exp Physiol* 26, 165–179.
- Shereff, R. H., Harwell, W., Lieberman, P., Rosenberg, E. W. & Robinson, H. 1973. Effect of beta adrenergic stimulation and blockade on immediate hypersensitivity skin test reactions. *J Allergy Clin Immunol* 52, 328–333.
- Sörenby, L. 1974a. Inhibition of the antigen-induced release of histamine from guinea-pig lung by terbutaline. *Acta Pharmacol Toxicol* 34, 267–272.
- 1974b. On the immunological histamine release from guinea-pig lung and its inhibition by isoprenaline. *Acta Pharmacol Toxicol* 34, 273–383.
- 1975. The β -adrenoceptors of the lung mediating inhibition of antigen-induced histamine release. *Eur J Pharmacol* 30, 140–147.
- 1977. A new β -adrenoceptor stimulant, preferably with antianaphylactic effect. Thesis for Ph.D. degree, Uppsala.
- Svensson, G. 1974. Unpublished data.
- Svensson, G., Hegardt, B. & Löfkvist, T. 1980. Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. I. Normal persons and hay fever patients in asymptomatic period. *Acta Otolaryngol* (Stockh), in press.
- Tuft, L. & Brodsky, M. L. 1936. The influence of various drugs upon allergic reactions. *J Allergy* 7, 238–248.

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INFLUENCE OF A β -ADRENOCEPTOR STIMULANT, KWD 2131,
ON NASAL HISTAMINE PROVOCATION TESTS

Rhinomanometric evaluations in normal persons and
patients with hay fever

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INTRODUCTION

An antianaphylactic effect has been attributed to β -adrenoceptor stimulants in animal and man (cf. Holroyde et al., 1977). A new β -adrenoceptor stimulant, KWD 2131, partially blocked increasing nasal airway resistance at nasal allergen provocations (Svensson, 1980). This blocking might be a mast-cell-stabilizing effect, i.e. reduced release of mediators from mast cells at the allergen challenges, and/or an inhibition of the effects from released mediators.

Several substances are released from the mast cells at reagin-dependent reactions. A main part of the action of the mediators is attributed to histamine. Consequently, this substance was selected for the present experiments. Among other actions, histamine increases the microvascular leakage, while β -adrenoceptor stimulants have been shown to reduce such an oedema formation (Green, 1972; Svensjö et al., 1976; O'Donnell & Persson, 1978; Persson et al., 1978, 1979). There have recently been speculations about a favourable oedema-reducing capacity of β -adrenoceptor stimulants at treatment of mediator-induced asthma with these substances (O'Donnell & Persson, 1978; Persson et al., 1978, 1979).

The present experimental study has been performed to clarify the mode of action of KWD 2131 at nasal allergen challenges. It may have reduced the release of histamine and/or decreased the microvascular leakage due to histamine. A reduction of histamine-induced increase of nasal airway resistance should indicate an inhibition of vascular effects of histamine, while no effect indicates a mast-cell-stabilizing action.

Histamine inhalations have been shown to induce greater

responses in the lower airways of asthmatic patients than of normal persons (Curry, 1946; Laitinen, 1974), while skin test reactions induced by histamine have been comparable in atopic and non-atopic individuals (Farmer, 1945; Bryant & Burns, 1976; McLean et al., 1977). An increased (Grobler, 1966; Okuda, 1977 a) as well as an unchanged (McLean et al., 1977; Guercio et al., 1979) nasal reactivity to histamine have, however, been reported in patients with allergic rhinitis in comparison to non-atopic subjects. In view of the differences of opinion it seemed to be of interest to make further investigations of the nasal response to histamine.

MATERIAL AND METHODS

The trial was conducted over a pollen-free period of three months and involved a total of 22 subjects (11 normal persons and 11 patients with allergic rhinitis). The normal volunteers (7 males and 4 females) aged 17 - 34 years (average 27 years), had never had symptoms simulating allergic rhinitis, dermatitis, urticaria or bronchial asthma and had no heredity for these diseases. Analysis of IgE/serum with PRIST^R was within normal limits. The patients with seasonal allergic rhinitis (8 males and 3 females) aged 18 - 27 years (average 22 years), were asymptomatic during the trial. All of them were sensitive to grass pollen as shown by positive skin test and positive provocation test, and had suffered from hay fever during the last two seasons at least.

Nasal histamine provocations were performed with the disc method (Okuda, 1977 b) which involves small paper discs (squares with sides of 8 mm) soaked in 0.05 ml histamine chloride (1 mg/ml) and attached to the anterior part of both lower turbinates. The duration of each challenge was 5 min.

The substances under investigation were 1-(3,5-dihydroxy-phenyl)-2- [(1,1-dimethyl-2-hydroxyethyl)-amino] ethanol sulphate (KWD 2131, AB Draco, Lund) and isotonic saline solution (placebo). The dosage of KWD 2131 was 5 mg to each nasal cavity, based on experiences of prior investigations (Svensson, 1980; Svensson et al., 1980). The preparations were applied locally as nose drops from a pipette in two equal portions (2 x 0.08 ml) to each nasal cavity with a time interval of 2 min between the portions. During the drug application the subject was sitting with his/her head tilted backwards and laterally

for administration against the lower turbinate. Placebo was administered in the same volume and manner.

After each application the subject was questioned regarding any taste of drug, for evaluation of nasal and/or pharyngeal deposition of the drugs. Experiments with suspected pharyngeal deposition were put off to some other day. When used, the drugs had the same temperature as the testing room, i.e. 22-23°C. In the meantime they were stored in a refrigerator (4-8°C).

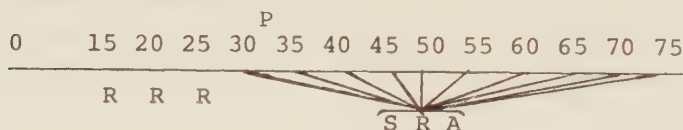
The study included four visits with nasal histamine challenges - two provocations without any pretreatment with drugs for determination of differences of nasal reactivity to histamine in atopic and non-atopic individuals, and two provocations preceded by treatment with KWD 2131 and placebo in a randomized double-blind cross-over manner for evaluation of the antihistamine effect of the substances. At a fifth visit the mechanical effect of the discs was investigated. On this occasion, instead of histamine solution, discs soaked in Coca's solution were applied to the anterior part of the lower turbinates for 5 min. The interval between each challenge was at least three days.

Each subject was interviewed and medically examined (rhinoscopy for evaluation of nasal obstruction and secretion) before entry into the trial as well as before, during and after each testing. All subjects were without nasal symptoms before each provocation and free from drugs.

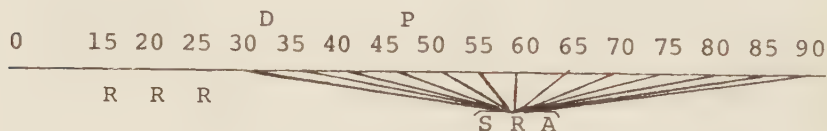
The nasal patency was evaluated with posterior rhinomanometry. The first rhinomanometric determination was done after 15 minutes' adaptation to the testing room and repeated every 5 min. The preparations were ad-

ministered after 30 minutes' stay in the testing room. At visits without pretreatment, the provocation was performed at this time or else after 45 min. The condition of the nose was also recorded rhinoscopically as to the presence of oedema and secretion on a 0-3 scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) before and every 5 min after application of the preparations and the nasal challenges. This examination was performed after the rhinomanometric evaluation. Also, the patients' subjective opinion of nasal symptoms was recorded on a 0-3 scale. The test procedure is given schematically as follows:

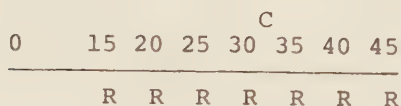
Visit 1 and 4:



Visit 2 and 3:



Visit 5:



P = Provocation with histamine
D = Drug application
C = Coca disc application
R = Rhinomanometry
S = Patients' subjective opinion
A = Anterior rhinoscopy

Rhinomanometry

The nasal airway resistance in both nasal cavities together (total nose) was determined during spontaneous breathing with the aid of posterior rhinomanometry in a sitting position, using the technique of Broms (1980) for evaluation of the results. Thus, an angle v_2 , as a measure of nasal airway resistance, was calculated.

Increasing values of v_2 denote increasing nasal airway resistance.

The difference in angle v_2 was analysed statistically with Student's t-test.

Because of the subjects' adaptation to the experimental situation, no statistical analyses were done until after 30 minutes' stay in the testing room.

The study was approved by the Ethical Committee of the University of Lund and informed consent was obtained from all patients.

RESULTS

Fig. 1 shows the mean values of nasal airway resistance (expressed as angle v_2) in normal subjects and patients with seasonal allergic rhinitis, before and after nasal histamine challenges, with the participants in a sitting position during the first and fourth visit. The groups were comparable as regards nasal airway resistance, and no significant differences were found between the groups before the histamine provocations. The nasal application of histamine was followed by marked increases in nasal airway resistance. Compared with the values before the challenges, these increases were all statistically significant.

The mean values of v_2 for the allergic patients were overall somewhat higher than those for the normal subjects, but only occasional significant differences between the groups were demonstrated (Table I). Analyses of the rhinoscopic findings provided a uniform pattern, i.e. only isolated significant differences between allergic and non-allergic volunteers (Table II). The number of sneezings as well as the participants' subjective opinion of nasal stuffiness, secretion and itching after histamine administration were similar in both groups and only some occasional significant differences between the patients and the normal subjects were revealed.

Fig. 2 gives the mean values of nasal airway resistance (expressed as angle v_2) before and after nasal application of KWD 2131 or placebo as well as after the consecutive histamine provocation in both groups of volunteers. The means for the allergic patients were generally higher than those for the normal persons but only isolated significant differences were demonstrated be-

tween the groups (Table I). Analyses of the participants' subjective opinion of nasal stuffiness, secretion and itching, the number of sneezings as well as the rhinoscopic findings as regards obstruction (Table II) and secretion (Table II) gave a similar pattern.

The influence of pretreatment with KWD 2131 and placebo on nasal airway resistance before and after histamine challenges for normal persons and allergic patients also appears from Fig. 2. No statistically significant differences were found between the substances, either in the atopic or in the healthy group. Analyses of the subjective and rhinoscopic parameters after the different forms for pretreatment gave the same results in both groups of volunteers.

The application of discs, soaked in Coca's solution, induced only minor and transitory increases of nasal airway resistance.

DISCUSSION

Nasal histamine provocations are used experimentally to increase nasal secretion (Ingelstedt & Ivstam, 1949; Okuda, 1975; Konno & Togawa, 1979) as well as nasal obstruction in order to evaluate effects of nasal decongestants (Aschan et al., 1958; Britton et al., 1978; Cockcroft et al., 1979). Reports considering the effects of nasal administration of histamine on subjects with and without nasal allergy are contradictory. McLean et al. (1977) and Guercio et al. (1979) recorded equal nasal reactions to aerosolized histamine in non-atopic individuals and patients with allergic rhinitis. Grobler (1966), however, noted stronger nasal reactions to histamine in persons with "nasal complaints" than without, but the subjects were not allergologically examined. Okuda (1977 a) too, found a higher incidence of sneezing, watery secretion and mucous membrane swelling after histamine spray in patients with allergic rhinitis than in non-allergic controls.

Experiences from a previous study (Svensson, 1980), when paper discs were used at nasal allergen provocation tests were adopted here in the challenge of the nasal mucosa with histamine. The recorded effects of histamine (number of sneezings, the participants' subjective opinion of different parameters, rhinoscopic observations as well as rhinomanometric determinations) were generally without significant differences between the normal controls and the patients with allergic rhinitis. This is in agreement with the observations of McLean et al. (1977) and Guercio et al. (1979) despite different modes for administration of histamine. The divergent results published by Okuda (1977 a) may be due to different methods. Firstly, he based his results on rhinoscopy, while in this study as well as

in those by McLean et al. (1977) and Guercio et al. (1979) rhinomanometry was used for a more objective evaluation. Secondly, it is not evident from the report of Okuda (1977 a) if the patients suffered from perennial or seasonal allergic rhinitis, and if they were symptomatic or free from symptoms before the challenges. Symptomatic patients may have more vigorous reactions than asymptomatic controls.

The demonstrated equality in the response to histamine in normal subjects and patients with allergic rhinitis bears a close resemblance to the results of skin tests with histamine in non-allergic and allergic individuals, indicating equal sensitivity of histamine receptors (Farmer, 1945; Bryant & Burns, 1976; McLean et al., 1977). In the lower airways, however, histamine elicits stronger responses in asthmatic patients than in normal persons (Curry, 1946; Laitinen, 1974). The lower airways of asthmatic patients are hyperreactive to many agents. Stimulation of receptors sensitive to irritants initiate vagal reflexes with bronchoconstriction as a result (cf. Reed & Townley, 1978). Thus, at pulmonary inhalation, histamine may evoke a local action as well as induce reflex responses (cf. Gold, 1978).

KWD 2131, a new β -adrenoceptor stimulant (Sörenby, 1977), was recently shown by us (Svensson, 1980) to have a prophylactic effect at nasal allergen provocations in asymptomatic patients with hay fever. An antianaphylactic ability or an inhibition of histamine-induced effects of KWD 2131 might explain the prophylactic effect of the substance. The absence of protective capacity against histamine-evoked effects with KWD 2131 in the present study is an indirect evidence of a mast-cell-stabilizing property of the substance at

the allergen challenges. Corresponding results have also been obtained with KWD 2131 at skin test reactions with allergen and histamine (Hegardt & Arner, 1981).

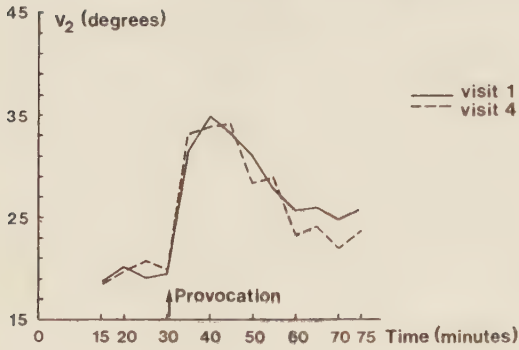
The clinical value of KWD 2131 has been evaluated during a pollen season and will be presented in a subsequent report (Svensson, 1981).

SUMMARY

Nasal histamine provocations have been performed in 11 asymptomatic (out of season) patients with hay fever and in 11 normal controls. Posterior rhinomanometry has been used for objective evaluation. The histamine challenges induced nasal symptoms as well as increased nasal airway resistance. The differences in response between the two groups of subjects were not significant.

KWD 2131, a β -adrenoceptor stimulating drug and ascribed antiallergic effect in a prior allergen provocation study, did not block the effects of histamine challenges in a randomized placebo-controlled double-blind cross-over evaluation. The absence of protective action against histamine-induced effects with KWD 2131 supports a mast-cell-stabilizing effect of the substance at allergen provocations.

NORMAL PERSONS



PATIENTS WITH ALLERGIC RHINITIS

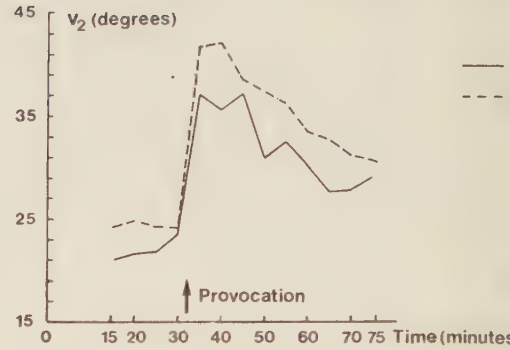
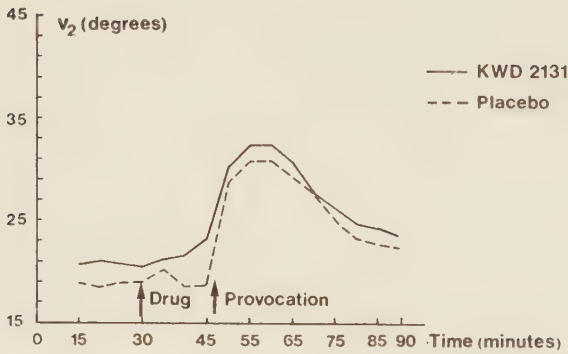


Fig. 1. Nasal airway resistance versus time in normal controls and in patients with seasonal allergic rhinitis before and after nasal histamine challenges.

NORMAL PERSONS



PATIENTS WITH ALLERGIC RHINITIS

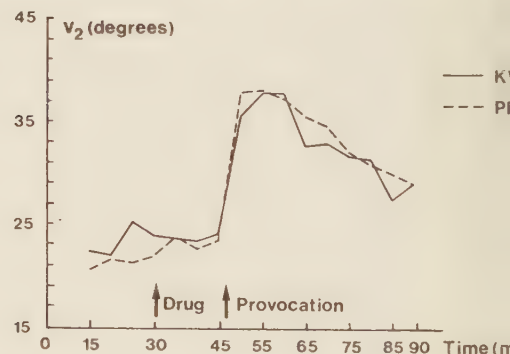


Fig. 2. Nasal airway resistance versus time in normal controls and in patients with seasonal allergic rhinitis before and after nasal application of KWD 2131 or placebo as well as nasal histamine challenges.

Table I. Comparison of v_2 -values from healthy volunteers (HV) with those from patients with seasonal allergic rhinitis (AR) at different time interval after histamine provocation

Minute after histamine provocation	HV - AR Visit 1 (No pretreatment)	HV - AR Visit 4 (No pretreatment)	HV - AR Pretreatment with placebo	HV - AR Pretreatment with KWD 2131
5	n.s.	n.s.	n.s.	$p < 0.05$
10	n.s.	n.s.	n.s.	n.s.
15	n.s.	n.s.	n.s.	n.s.
20	n.s.	n.s.	n.s.	n.s.
25	n.s.	n.s.	n.s.	n.s.
30	n.s.	$p < 0.05$	n.s.	n.s.
35	n.s.	n.s.	n.s.	$p < 0.05$
40	n.s.	n.s.	n.s.	n.s.
45	n.s.	n.s.	n.s.	$p < 0.05$

n.s. = not significant differences

Table II. Comparisons of rhinoscopic findings as regards nasal obstruction (NO) and secretion (NS) in healthy volunteers (HV) with those in patients with seasonal allergic rhinitis (AR) at different time interval after histamine provocation

Minute after histamine provocation	HV - AR Visit 1 (No pretreatment)		HV - AR Visit 4 (No pretreatment)		HV - AR Pretreatment with placebo		HV - AR Pretreatment with KWD 2131	
	NO	NS	NO	NS	NO	NS	NO	NS
5	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
10	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
15	n.s.	p<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
20	p<0.05	n.s.	p<0.05	n.s.	n.s.	n.s.	n.s.	n.s.
25	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	p<0.05	n.s.
30	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
35	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

n.s. = not significant differences

REFERENCES

- Aschan, G., Drettner, B. & Ronge, H.E. 1958. A new technique for measuring nasal resistance to breathing, illustrated by the effects of histamine and physical effort. Ann Acad Regiae Sci Ups 2, 111-126.
- Britton, M.G., Empey, D.W., John, G.C., McDonnell, K.A. & Hughes, D.T.D. 1978. Histamine challenge and anterior nasal rhinometry: Their use in the assessment of pseudoephedrine and triprolidine as nasal decongestants in subjects with hayfever. Br J Clin Pharmacol 6, 51-58.
- Broms, P. 1980. Rhinomanometry. Thesis, University of Lund.
- Bryant, D.H. & Burns, M.W. 1976. The relationship between bronchial histamine reactivity and atopic status. Clin Allergy 6, 373-381.
- Cockcroft, D.W., MacCormack, D.W., Tarlo, S.M., Hargreave, F.E. & Pengelly, L.D. 1979. Nasal airway inspiratory resistance. Am Rev Respir Dis 119, 921-926.
- Curry, J.J. 1946. The action of histamine on the respiratory tract in normal and asthmatic subjects. J Clin Invest 25, 785-791.
- Farmer, L. 1945. Evaluation of the histamine intradermal test as a general indicator of allergy. J Allergy 16, 44-47.
- Gold, W.M. 1978. Anticholinergic drugs. In Allergy. Principles and Practice. Vol. I. (ed. E.Middleton, Jr., C.E.Reed and E.F.Ellis), pp. 499-530. The C.V.Mosby Company, Saint Louis.
- Green, K.L. 1972. The anti-inflammatory effect of catecholamines in the peritoneal cavity and hind paw of the mouse. Br J Pharmacol 45, 322-332.

- Grobler, N.J. 1966. Reactivity of the nasal respiratory mucosa (a clinical and epidemiological study). Thesis. Drukkerij van Denderen, Groningen.
- Guercio, J., Sakethkoo, K., Birch, S., Fernandez, R., Tachmes, L. & Sackner, M.A. 1979. Effect of nasal provocation with histamine, ragweed pollen and ragweed aerosol in normal and allergic rhinitis subjects. Am Rev Respir Dis 119, Suppl 4, 69.
- Hegardt, B. & Arner, B. 1981. Inhibition of allergen-induced intracutaneous reactions by a new β -agonist, KWD 2131, and by terbutaline. Accepted for publication in Eur J Respir Dis.
- Holroyde, M.C., Burka, J.F. & Eyre, P. 1977. Auto-modulation of release of pharmacological mediators of immediate (Type I) hypersensitivity. A review. Agents Actions 7, 421-430.
- Ingelstedt, S. & Ivstam, B. 1949. The source of nasal secretion in infectious, allergic, and experimental conditions. Acta Otolaryngol (Stockh) 37, 451-455.
- Konno, A. & Togawa, K. 1979. Role of the vidian nerve in nasal allergy. Ann Otol Rhinol Laryngol 88, 258-266.
- Laitinen, L.A.I. 1974. Histamine and metacholine challenge in the testing of bronchial reactivity. Medical dissertation, Helsinki. Scand J Respir Dis (Suppl) 86.
- McLean, J.A., Mathews, K.P., Solomon, W.R., Brayton, P.R. & Ciarkowski, A.A. 1977. Effect of histamine and methacholine on nasal airway resistance in atopic and nonatopic subjects. Comparison with bronchial challenge and skin test responses. J Allergy Clin Immunol 59, 165-170.
- O'Donnell, S.R. & Persson, C.G.A. 1978. β -adrenoceptor mediated inhibition by terbutaline of histamine effects on vascular permeability. Br J Pharmacol 62, 321-324.

- Okuda, M. 1975. IgE and IgE antibody to mite in nasal fluid. ORL 37, 344-355.
- Okuda, M. 1977 a. Mechanisms in nasal allergy. Part I. ORL Digest 39, 26-33.
- Okuda, M. 1977 b. Basic study of nasal provocative test. First report: Side, site of the nose, size of site and allergen amount. Arch Otorhinolaryngol 214, 241-246.
- Persson, C.G.A., Ekman, M. & Erjefält, I. 1978. Terbutaline preventing permeability effects of histamine in the lung. Acta Pharmacol Toxicol (Kbh) 42, 395-397.
- Persson, C.G.A., Ekman, M. & Erjefält, I. 1979. Vascular anti-permeability effects of β -receptor agonists and theophylline in the lung. Acta Pharmacol Toxicol (Kbh) 44, 216-220.
- Reed, C.E. & Townley, R.G. 1978. Asthma. Classification and pathogenesis. In Allergy. Principles and Practice. Vol. II. (ed. E.Middleton, Jr., C.E.Reed and E.F. Ellis), pp. 659-677. The C.V.Mosby Company, Saint Louis.
- Sörenby, L. 1977. Studies on the inhibition of anaphylactic histamine release from the guinea-pig lung by β -adrenoceptor stimulants. Thesis, Uppsala University.
- Svensjö, E., Persson, C.G.A. & Arfors, K.-E. 1976. Effects of bradykinin and terbutaline on macromolecular leakage and its relation to other microvascular effects. Microvasc Res 11, 425.
- Svensson, G. 1980. Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. II. Nasal provocation tests with hay fever patients in asymptomatic period. Acta Otolaryngol (Stockh) 90, 130-138.
- Svensson, G. 1981. Topical treatment of seasonal allergic rhinitis with a β -adrenoceptor stimulant (KWD 2131). In manuscript.

Svensson, G., Hegardt, B. & Löfkvist, T. 1980. Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. I. Normal persons and hay fever patients in asymptomatic period. Acta Otolaryngol (Stockh) 90, 297-303.

TOPICAL TREATMENT OF SEASONAL ALLERGIC RHINITIS
WITH A β -ADRENOCEPTOR STIMULANT (KWD 2131)

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INTRODUCTION

An antiallergic effect in animal as well as in man has been attributed to sympathomimetic amines (cf. Holroyde et al., 1977; Sörenby, 1977; Martin et al., 1979; Strandberg et al., 1979). A new β -adrenoceptor stimulant, KWD 2131, was recently shown to have a prophylactic effect on allergen-provoked nasal obstruction in hay-fever patients - out of season - studied rhinomanometrically (Svensson, 1980). In a prior study (Svensson et al., 1981) KWD 2131 did not block the action of histamine in the nasal tissue. Probably, the drug acts as a mast-cell stabilizer. The present report deals with the clinical use of KWD 2131 during the hay-fever season.

MATERIAL AND METHODS

Altogether 27 patients, 23 males and 4 females, aged between 14 and 52 years (average 27 years), were included in the trial, all of them being sensitive to grass pollen, as shown by positive skin test or positive provocation test (Löfkvist & Svensson, 1975). All had suffered from hay fever during at least the last two seasons, and prior medication with antihistamines or disodium cromoglycate or beclomethasone dipropionate or hyposensitization had been insufficient for required relief of the allergic symptoms. No subject currently on a hyposensitization course was included. The characteristics of the patients are provided in Table I.

The trial was conducted over a 4-week period between mid-June and mid-July during the summer of 1979.

The study was of a randomized, placebo-controlled, double-blind type and the design made cross-over evaluations as well as comparisons of parallel groups possible. Fourteen patients started with a 2-week treatment period with 1-(3,5-dihydroxyphenyl)-2-[(1,1-dimethyl-2-hydroxyethyl)-amino] ethanol sulphate (KWD 2131, AB Draco, subsidiary of AB Astra, Sweden), followed by 2 weeks' placebo (saline solution) treatment. The other 13 patients were treated in the reverse order. KWD 2131 and placebo were distributed in identically equal packings, and were administered as nose drops. The dosage was 3 drops to each nasal cavity, repeated after 2 minutes, 3 times daily during both the placebo period and the KWD 2131 period. Six drops (3 x 2) of the active substance corresponds to 5 mg KWD 2131, which means a total dose of 30 mg in a 24-hour period. The dosage was based on experiences from prior investigations (Svensson, 1980; Svensson et al., 1980). A supply of tablets containing

antihistamine and sympathomimetic substance (brompheniramine + phenylpropanolamine - Lunerin^R mite /AB Draco, Sweden) was issued to each patient with instructions to use them only if symptoms were so severe as to make the medication indispensable. Treatment with other drugs was not allowed.

Each subject recorded the following symptoms on a daily diary card: nasal blocking, running, itching and eye symptoms, on a scale 0-3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms). The number of sneezing attacks were also recorded on a 0-3 scale (0 = no attacks, 1 = 1-5 attacks, 2 = 6-15 attacks, 3 = more than 15 attacks in a 24-hour period). If it was necessary to take Lunerin^R mite tablets, the number was entered on the diary card too. The patients were also requested to enter suspected and convincing side effects on the diary card.

Each patient was interviewed and medically examined (routine ENT examination) before entry into the trial and on the last day of both the KWD 2131 and the placebo period. The condition of the nose was recorded as to the presence of oedema and secretion, again on a 0-3 scale.

Conventional β -adrenoceptor stimulants are shown to increase the content of glucose in blood, be metabolized to a varying degree in the liver and excreted in urine in different forms. Therefore haematological analysis (haemoglobin, leucocyte count) and examination of protein (Albustix^R) and glucose (Clinistix^R) in urine as well as estimations of serum enzymes (alkaline phosphatase, glutamyltransferase, aspartate amino transferase, alanine amino transferase) and bilirubin/s were also carried out on these occasions.

On the last day of the both treatment periods, the patients' subjective evaluation of the therapeutic effect was recorded as answers to the following questions:

1. Were your nasal symptoms adequately controlled?
2. Do you regard the treatment with the nose drops as a success or a failure?
3. Have you experienced any side effects of the treatment?

At the last examination, the patients' opinion as to which of the treatment periods had given the least nasal trouble, or whether they had found no difference between the two periods, were entered on the protocol.

Data on pollen counts were obtained by means of a Burkard^R slit sampler, placed at the ENT Clinic, Malmö General Hospital. The identification of the pollen was performed at the Botanical Institution, University of Göteborg.

Statistical methods

The data obtained from the diary cards and medical examinations were subjected to statistical analysis with t-test.

The study was approved by the Ethical Committee of the University of Lund and informed consent was obtained from all patients.

RESULTS

The summer of 1979 may be regarded as medium-good with respect to the weather. During the first part of the investigation, it was warm and sunny, but during the second part the weather changed to lower temperature and cloudiness, mostly without rain (Ehde, 1979). The grass pollen season began at about the normal time.

- A couple of days before the start of this trial the pollen count showed a peak with about 30 grass pollen/m³ air. During the first week the count reached 8 grass pollen/m³ (Fig. 1). The highest grass pollen content (about 30-60 grass pollen/m³ air) was recorded during the second week of the trial. A marked decrease took place on passing to week 3, i.e. at the same time as the patients shifted medication from placebo to KWD 2131 or vice versa. During the third and fourth weeks the pollen count was low with 3 small peaks (26, 19, 22 grass pollen/m³ air, respectively). The total count of grass pollen during each week was 31, 194, 90 and 66 grass pollen/m³ air, respectively.

Fig. 2 shows the mean scoring as far as the different symptoms are concerned. The patients experienced the symptoms as mild with the exception of rather intense nasal obstruction and secretion during the second week. Generally, the scores were higher during the first part of the trial and especially during the second week.

All patients participating in the trial completed the treatment with three exceptions. One patient left the investigation due to insufficient effect of the treatment, the second patient due to intervening illness, and the third due to side effect (tremor).

The patients' subjective evaluation of the treatment

with placebo and KWD 2131 after each treatment period did not reveal any certain difference between the two forms of medication. Eighteen patients out of 24 experienced the treatment during the second period as more successful than during the first period, independently of the type of medication. Two patients did not find any differences between the periods and four patients preferred the first period. These six patients were all treated with KWD 2131 during the first part of the study.

Analysis of the notes on the diary cards with the patients arranged in parallel groups did not reveal any certain difference in symptom-relieving capacity between KWD 2131 and placebo. Special attention was paid to days with different amounts of grass pollen. During the days with the highest pollen count, i.e. day 10-14 (average 35 grass pollen/m³ air) as well as during days with 29-20, 19-10 and 9-0 grass pollen/m³, no significant differences were documented between treatment with KWD 2131 and placebo.

At the rhinoscopic examination no differences as regards oedema and secretion were observed. The use of Lunerin^R mite was low (Fig. 2) and without significant differences during both periods.

No certain side effects were revealed except tremor in one patient on KWD 2131. All laboratory analyses (haemoglobin, white cell count as well as hepatic and renal function tests) were within normal limits before and after each period of treatment.

DISCUSSION

β -adrenoceptor stimulants are often used in the treatment of asthma due to their bronchorelaxating ability. Side effects, such as tachycardia and tremor, which may restrict treatment with high doses, are not uncommon. An antianaphylactic effect, i.e. reduced release of histamine from mast cells at reagin-mediated reactions, is also attributed to β -adrenoceptor stimulants (cf. Holroyde et al., 1977; Martin et al., 1979). KWD 2131 is a new β -adrenoceptor stimulant with a mainly antianaphylactic effect and low tracheorelaxating, tremor-producing and chronotropic properties in animal (Sörenby, 1977) as well as human (Strandberg et al., 1979; Hegardt et al., 1980; Pegelow & Strandberg, 1980; Svensson, 1980; Svensson et al., 1980, 1981) experiments.

A prior rhinomanometric study (Svensson, 1980), including nasal pretreatment with KWD 2131 followed by nasal provocations with pollen, had revealed a prophylactic effect of the substance. However, rhinoscopic examination and the patients' subjective opinion could not reveal such an effect. Thus, the clinical value of KWD 2131 in allergic rhinitis was not established and had to be evaluated during the hay-fever season.

The present study was carried out during four weeks in June and July, i.e. at the hay-fever season in Sweden. The difference in grass pollen counts during the first and second period of the trial precluded cross-over evaluations. The statistical analyses had to be based on comparisons of parallel groups. This was suitable as the patients' characteristics in the two groups agreed fairly well (Table I). This grouping of the subjects reduced the number of patients in each treatment category. However, the quantity of volunteers obtained

in each group was still considered enough to reveal differences between a clinically useful substance and placebo.

Small amounts of pollen induce allergic symptoms. Three to five grass pollen/m³ air are sufficient to provoke a hay-fever attack in highly sensitive subjects (Grone-meyer, 1967), more than 10 grass pollen elicit symptoms in 10% of allergic patients (Hyde, 1972) and at 50 grass pollen all patients are symptomatic (Davies & Smith, 1973). In the present study, the patients also noted symptoms in a degree worth studying - even in days with a low count of grass pollen. However, neither in days with great amounts of grass pollen, nor in those with low amounts was there any apparent difference in symptoms between patients treated with 5 mg KWD 2131 three times a day and placebo. Higher doses of KWD 2131 would perhaps induce a more favourable relief of nasal symptoms, but such an increase of the dose seems to be restricted. Already in the given dose, one patient left the trial due to a general side effect - tremor.

The sum of data collected in this study do not support a clinical effect of KWD 2131, i.e. a result contrary to that presented in a preceding rhinomanometric study (Svensson, 1980). An explanation of this disagreement may be a higher sensitivity in rhinomanometric examinations than in the patients' subjective evaluations. According to Cohen (1978) patients with nasal congestion due to common cold note relief when treatment improves their flow/resistance values by at least 15-20%. KWD 2131 decreased nasal airway resistance by 20-30% at the nasal provocations with allergens (Svensson, 1980), which seemed promising. However, the negative findings in the present study give rise to doubts about the validity of the statement of Cohen at recommenda-

tions for clinical testing of a drug. There seems to be a demand for higher figures for the improvement of nasal passage.

For practical reasons rhinomanometry was not used and could scarcely have added further relevant data - rhinomanometry is a rather time-consuming examination and comparisons between the effect of KWD 2131 and placebo should, due to exposure of varying amount of pollen, have been performed day by day.

Antihistamines reduce the allergic symptoms and may mask a weak effect of the substance to be investigated. However, antihistamines have to be used due to ethical demands. The use of Luner^Rin mite in this study was limited and equal in both treatment groups, and therefore did not seriously affect the results.

A final comment deals with the second part of the trial, when in spite of low counts of pollen most patients had definite symptoms. The explanations might be threefold. Firstly, due to the selection our patients may be more sensitive to grass pollen than patients with hay fever as a whole. Secondly, the absolute amounts of pollen are representative only of the counting place (Hyde, 1972; Solomon & Mathews, 1978; Leuschner & Boehm, 1979), and those patients who live about 20 km away might have had higher expositions. The third factor may be the so-called "priming effect" (Connell, 1969), i.e. increased reactivity of the nasal mucosa to symptom-provoking allergens after repeated expositions.

SUMMARY

During 4 weeks of the grass pollen season in the south of Sweden 27 patients with seasonal allergic rhinitis were treated topically with a β -adrenoceptor stimulant, KWD 2131, which in an earlier rhinomanometric study had shown a prophylactic effect at nasal allergen provocations in hay-fever patients. A clinical effect of KWD 2131 could not be documented in this randomized placebo-controlled, double-blind comparative study.

Table I. Patients' characteristics

Variable		Value or frequency for	
		KWD 2131-Placebo	Placebo-KWD
Age	Mean	28	25
	Range	14-52	15-41
Sex	Male	11	12
	Female	3	1
Duration	Mean	10	8
	Range	2-20	2-17

Treatment previous years:

Antihistamine	14	13
Disodium cromoglycate	5	5
Nasal applic. of steroids	4	6
General adm. of steroids	5	6
Hyposensitization	5	4

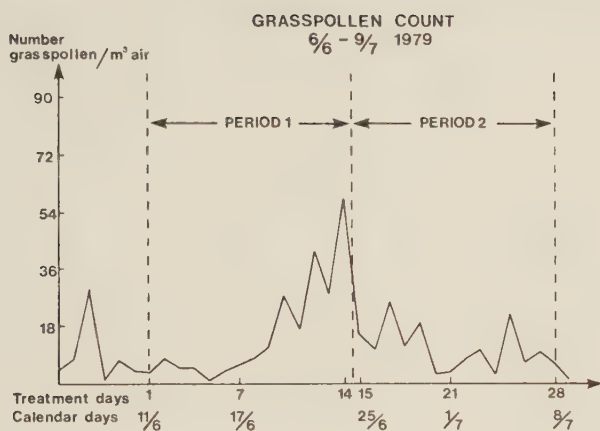


Fig. 1. Grass-pollen count before and during the investigation.

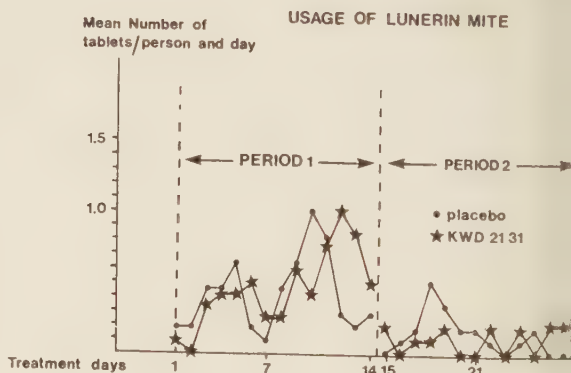
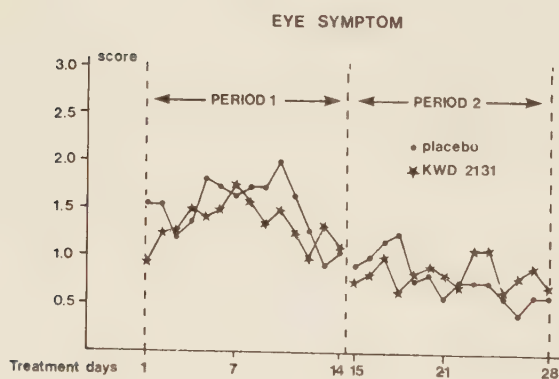
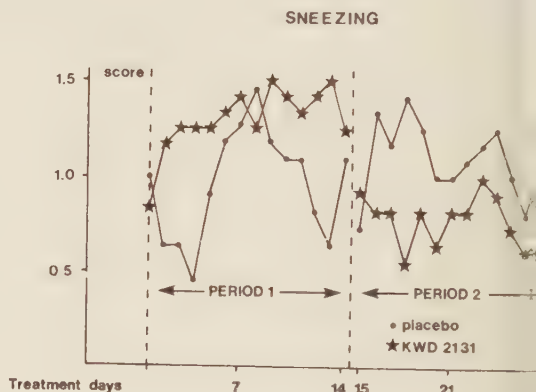
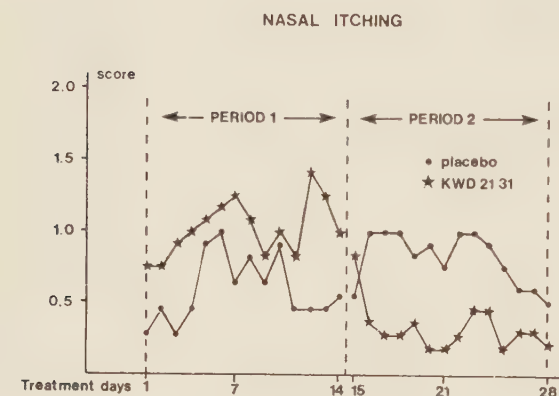
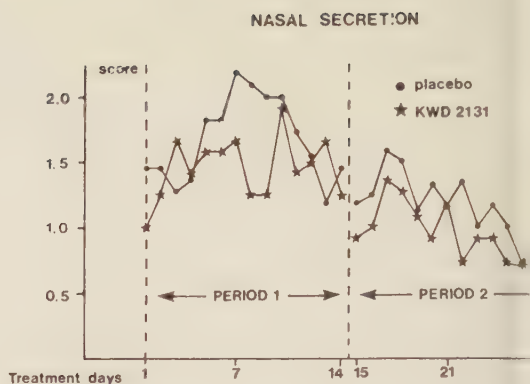
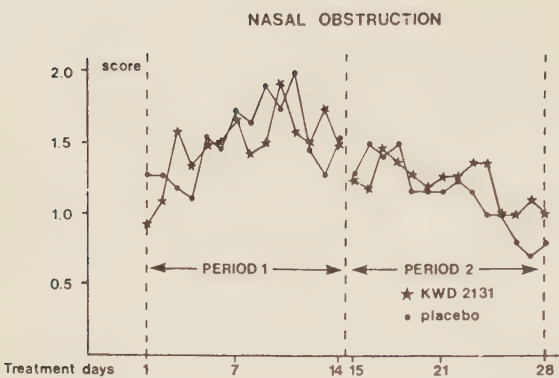


Fig. 2. Mean symptom score as regards nasal obstruction, nasal secretion, nasal itching, sneezing and eye symptoms as well as the usage of Lunerine^R mite during treatment with KWD 2131 and placebo in patients with seasonal allergic rhinitis.

REFERENCES

- Cohen, B.M. 1978. Clinical correlants of changes in nasal flow/resistance (Rn) measurements. Allergol Immunopathol (Madr) 6, 217-223.
- Connell, J.T. 1969. Quantitative intranasal pollen challenges. III. The priming effect in allergic rhinitis. J Allergy 43, 33-44.
- Davies, R.R. & Smith, L.P. 1973. Forecasting the start and severity of the hay fever season. Clin Allergy 3, 263-267.
- Ehde, M. (Sveriges Meteorologiska och Hydrologiska Institut, Malmö-Sturup Airport) 1979. Information about the weather in Lund, Sweden. Personal communication.
- Gronemeyer, W. 1967. Pollenallergie. In Lehrbuch der klinischen Allergie (ed. K.Hansen and M.Werner), pp. 167-178. G.Thieme Verlag, Stuttgart.
- Hegardt, B., Löwhagen, O. & Svedmyr, N. 1980. New β -agonist, KWD 2131, compared with terbutaline in asthmatics. Allergy 35, 105-112.
- Holroyde, M.C., Burka, J.F. & Eyre, P. 1977. Auto-modulation of release of pharmacological mediators of immediate (Type I) hypersensitivity. A review. Agents Actions 7, 421-430.
- Hyde, H.A. 1972. Atmospheric pollen and spores in relation to allergy. I. Clin Allergy 2, 153-179.
- Leuschner, R.M. & Boehm, G. 1979. Investigations with the 'Individual Pollen Collector' and the 'Burkard trap' with reference to hay fever patients. Clin Allergy 9, 175-184.
- Löfkvist, T. & Svensson, G. 1975. Cutaneous reactions to pollen extracts in patients with hay fever. Special references to grass pollen recommended for treatment in fixed combination. Acta Allergol (Kbh) 30, 96-105.

- Martin, G.L., Atkins, P.C., Dunskey, E.H. & Zweiman, B. 1979. Steroid and bronchodilator inhibition of antigen-induced bronchospasm and circulating histamine. J Allergy Clin Immunol 63, 162.
- Pegelow, K.-O. & Strandberg, K. 1980. Evaluation of the bronchodilating and anti-allergic properties of a β -adrenoceptor stimulant, KWD 2131, in asthmatic patients. Allergy 35, 509-519.
- Solomon, W.R. & Mathews, K.P. 1978. Aerobiology and inhalant allergens. In Allergy. Principles and Practice. Vol II. (ed. E.Middleton, Jr., C.E.Reed and E.F.Ellis), pp. 889-956. The C.V.Mosby Company, Saint Louis.
- Sörenby, L. 1977. Studies on the inhibition of anaphylactic histamine release from the guinea-pig lung by β -adrenoceptor stimulants. Thesis, Uppsala University.
- Strandberg, K., Pegelow, K.-O., Persson, C.G.A. & Sörenby, L. 1979. Anti-anaphylactic and bronchodilating action of a beta-adrenoceptor stimulator, KWD 2131, in human lung tissue. Allergy 34, 221-224.
- Svensson, G. 1980. Effects of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. II. Nasal provocation tests with hay fever patients in asymptomatic period. Acta Otolaryngol (Stockh) 90, 130-138.
- Svensson, G., Hegardt, B. & Löfkvist, T. 1980. Effect of topical use of β -adrenoceptor stimulants on nasal mucosa. Rhinomanometric evaluations in experiments with terbutaline and KWD 2131. I. Normal persons and hay fever patients in asymptomatic period. Acta Otolaryngol (Stockh) 90, 297-303.
- Svensson, G., Hegardt, B. & Löfkvist, T. 1981. Influence of a β -adrenoceptor stimulant, KWD 2131, on nasal histamine provocation test. Rhinomanometric evaluations in normal persons and patients with hay fever. Accepted for publication in Acta Otolaryngol (Stockh).

